APPLICATION OF A NEW TWO-STEP CONJUGATE ADDITION-ANODIC OXIDATION STRATEGY IN A SYNTHETIC APPROACH TO THE CYATHANE DITERPENES

By

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A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA

2003

Dedicated to my mother and to the memory of my father

ACKNOWLEDGMENTS

First, I thank my advisor Professor Dennis Wright for the opportunity and the guidance required to complete this work. I also thank Professors Tomas Hudlicky and Merle Battiste for their assistance in furthering my education.

I thank Dr. Ion Ghiviriga for multidimensional NMR analysis and instruction in the techniques required for these experiments. I thank Dr. Kalil Abboud for obtaining X-ray diffraction data and for interpreting the data. I thank the UF Mass Spectrometry services headed by Dr. David Powell. I thank the many teaching assistants in NMR, MS, and X-ray services at UF who, over the past 4 years, worked with the senior scientists mentioned above.

Many others assisted directly with this work. I specifically thank Dr. Dean Fry for introducing me to the techniques required to experiment with organic electrochemistry. Also, E. Hampton Sessions, Jeff Sperry, Sophie Klein, William Batson, and Ravi Orugunty all contributed to this work.

Claude Robotham, William Batson, Maria Estrella-Jimenez, Lynn Usher, and Ravi Orungunty all assisted in this work by their general efforts to support a chemistry research group. Josef Zezula and Ashwin Bharadwaj always were quick to let me borrow chemicals or advice. Dr. James Deyrup, Donna Balkcom, and Lori Clark all helped with my administrative needs. Personally, I thank my entire family and all of my friends for supporting me and giving me a life outside of chemistry.

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of the University of Florida in Partial Fulfillment of the
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APPLICATION OF A NEW TWO-STEP CONJUGATE ADDITION-ANODIC OXIDATION STRATEGY IN A SYNTHETIC APPROACH TO THE CYATHANE DITERPENES

By

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August 2003

Chair: Dr. Dennis L. Wright
Major Department: Department of Chemistry

A synthetic approach to the cyathane diterpenes is described. This approach relies on a [4+3] cycloaddition between an oxyallyl cation and a polycyclic furan, forming the 5-6-7 carbocyclic *nor* cyathane system. The synthesis of the polycyclic furan is accomplished by using a new two-step conjugate addition-anodic oxidation strategy. This new strategy was studied in general, and the results are reported.

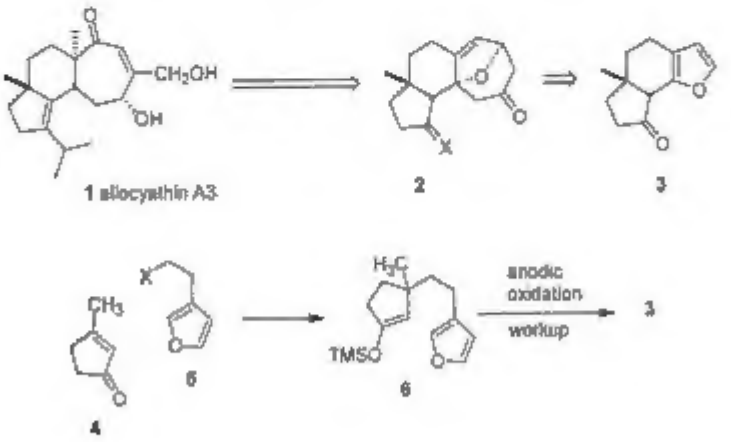
The new strategy relies on two steps. The first step is generation of a Grignard reagent from 2-(3-furyl)-bromoethane, and then copper(I) iodide is used to promote conjugate addition of the Grignard reagent to a cyclic α, β-unsaturated ketone. Chlorotrimethylsilane is present in the reaction to in order to form the silyl enolether and also serves to accelerate the reaction to β, β-disubstituted enones. The next step is oxidation of the silyl enolether in an electrochemical cell. Constant current electrolysis of the furan substituted silyl enolether in solutions of acetonitrile, 2-propanol, $LiClO_4$,

and 2,6-lutidine with a carbon anode forms a carbon-carbon bond between the furan and the enolether, generating an intermediate dihydrofuran acetal. The unstable dihydrofuran acetal reverts to the polycyclic furan upon workup with aqueous acid. Several different polycyclic furans were synthesized in order to study the stereoselectivity and general applicability of this method.

One of the new polycyclic furans synthesized and reported here serves as a precursor to the *nor* cyathane system. The A ring of the cyathanes is envisioned to arise from cyclopentenone. The B ring of the cyathanes is formed using our two-step strategy to form polycyclic furans. The furan ring then serves as a diene in a [4+3] cycloaddition reaction with an oxyallyl cation generated from the 1,1,3-trichloroacetone to form the C ring of the cyathanes. Attempts to introduce another key quaternary stereogenic center are also reported.

CHAPTER I
INTRODUCTION

An understanding of the practical science of forming chemical bonds is gained by attempting to synthesize a given target. A target can be selected for different reasons, both practical and academic. As our models for predicting the behavior of a biological system as a quasi-chemical system are becoming more accurate, synthesizing a biologically relevant organic target becomes a reasonable way to improve our understanding of bonding theory in complex molecular systems, both chemical and biological. We discuss our investigation of a target-oriented synthesis of naturally occurring organic compounds. In the course of this investigation a new synthetic method was explored and the results of the exploration are reported here.



Scheme 1

A retrosynthetic analysis can be used to visualize the synthesis of natural cyathane **1** from the tricyclic furan **3**. The furan **3** can be synthesized in useful quantities by using

the two-step strategy reported in this dissertation. This method was studied in general and several new compounds analogous to **3** are reported.

We targeted the compounds discussed in this dissertation because these natural products stimulate the biosynthesis of Nerve Growth Factor (NGF) *in vitro*.[1-6] Further studies have implicated some of these compounds in the signal transduction pathway for neurotrophin biosynthesis and other biochemical pathways.[7,8] We hope that useful therapeutics could be developed from this research. We wanted a synthesis that targets the natural products and analogous structures. We wanted analogues that cannot be obtained from the natural product itself, because their availability would allow a detailed study of the biological systems with which these compounds interact. Although no new biological or biochemical studies are reported in this dissertation, we discuss what is known about these compounds to show the usefulness of our synthetic strategy relative to the objective of analogue synthesis.

CHAPTER 2
HISTORICAL

The Cyathanes and Neurotrophins

Over 30 years ago a new fungus was discovered.[9] This fungus was named *Cyathus helenae* Brodie by the discoverers. The organic extracts of this fungus were found to have potent antimicrobial activity.[10] Purification of the active chemical species yielded several new diterpenes of similar structure.[11-16] These compounds were named cyathins, and the parent diterpene skeleton was named the cyathane ring system. Twenty years later the search for biologically active metabolites from the basidiomycetes *Hericium erinaceum*[1-3,5,17,18] and *Sarcodon scabrosus*[4,6,19] yielded new compounds, which were found to possess the same cyathane ring system.

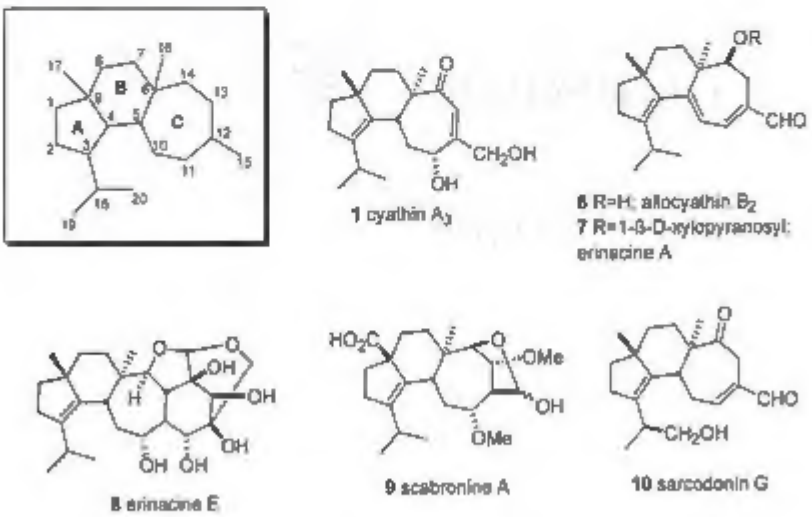


Figure 1. Representative cyathanes and the cyathane ring system.

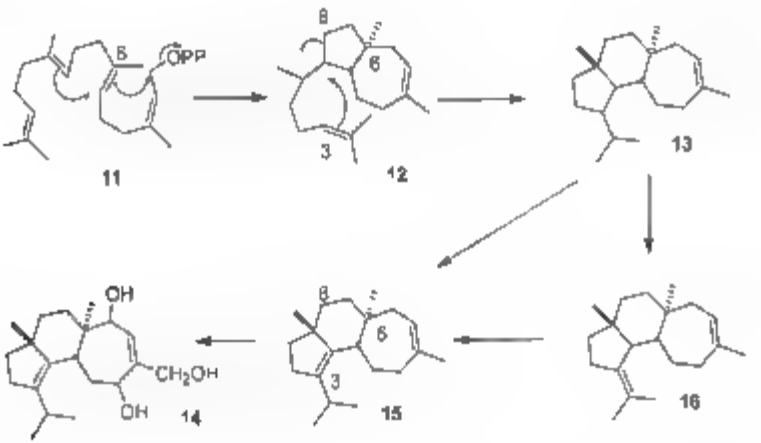
The cyathins where first isolated from the basidomycetes *Cyathus sp.* These tricyclic compounds all contained the same 20 carbon ring system. The relative and absolute stereochemistry was determined at this stage. Investigators searching for metabolites of basidomycetes with biological activity discovered the erinacines and scabronines. Many of the erinacines were determined to be composed of a cyathin aglycon with a xylose residue as the glycoside. Degradation products of some of the erinacines were matched to the natural cyathins. The scabronines and sarcodonins were found to be more highly oxidized cyathanes.

All of the cyathanes are derived from the same 5-6-7 tricyclic system. Twelve carbons form the ring system with two carbons present as angular methyl groups at the C6 and C9 stereogenic centers. A tertiary stereogenic center is present at C5. An isopropyl group is present at C3, and an additional carbon is present at C12.

Cyathane Biosynthesis

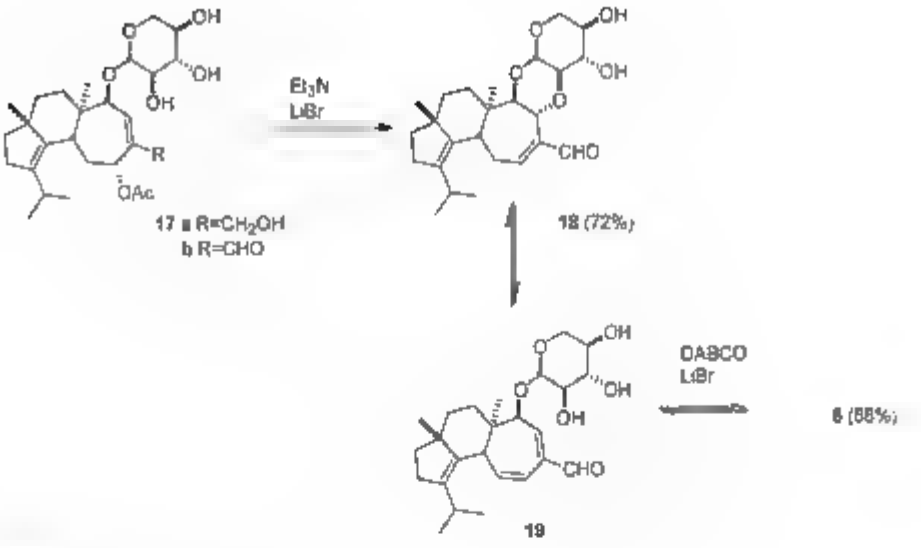
Ayer and coworkers[20] first studied the biogenesis of the cyathanes through ^{13}C-incorporation studies. *Cyathus earlei* was incubated with differentially enriched ^{13}C-acetate. After isolation of the diterpene **14**, the enriched positions were determined by analysis of the ^{13}C NMR spectrum. From this Ayer deduced that the most likely pathway to the cyathane system arises from the universal diterpene precursor geranylgeranyl pyrophosphate (**11**), which is ultimately derived from acetate. Cationic cyclization of **11** gives the bicyclic intermediate **12** (Scheme 2). Ring expansion of the cyclopentane through carbon-carbon bond migration and then ring closure gives the intermediate **13**. At this point there are alternative pathways to form the cyathane hydrocarbon **15**. The occurrence of the parent hydrocarbon **15** was proposed by Ayer and would require series of allylic oxidations to produce cyathatriol (**14**). Eventually hydrocarbon **15** was

obtained from the extracts of *Hericium erinaceum*,[24] and its structure confirmed by correlation to a degradation product of the triol **14**. Cell free synthesis of this hydrocarbon was also reported using the cellular extract. This synthesis was considered to be proof of a "cyathadiene synthase." A compound also isolated in microgram quantities and isomeric to cyathane **15** was assigned the structure **16**.



Scheme 2

The laboratory of Takeshi Sassa[17] investigated the biogenesis of the erinacines. The natural erinacine **17a** was converted into the natural erinacine **17b**, natural **18** and **6** (Scheme 3). The xlyoside **6** was isolated when **17b** was treated with DABCO-LiBr. In NMR experiments natural **18** was observed to form first. The formation of a compound whose structure was assigned as **19** is observed as well as **6**. After heating over an extended period of time, the erinacine **6** is formed as the exclusive product. Sassa and coworkers used the results of these experiments to argue that **17a** is a parental metabolite of all the cyathane xylosides.



Scheme 3

Neurotrophin Biosynthesis

Many of the cyathanes isolated from *Hericium sp* and *Sarcodon sp* where found to be stimulators of the biosynthesis of Nerve Growth Factor (NGF). The NGF protein is one of several neurotrophic agents, and has been found to be a regulator of other biological pathways. The peptide itself has been screened as a possible therapeutic, but is a poor drug substance due manly to its inability to cross the blood-brain barrier [23-24] The desire for synthetic cyathanes can be introduced with a quote from Saragovi and Gehring (page 93):[23]

> Neurotrophic activity is defined as the biological signal elicited by a family of polypeptides called neurotrophins, which are related in amino acid sequence and structure Impairment of the regulation of neurotrophins or their receptors has been postulated to be relevant to neurodegeneration, neuropathies, pain and cancer and provides a rationale for therapeutic intervention.

The use of use small molecule inducers of NGF biosynthesis is considered a possible treatment of neurodegenerative disorders. Not only is it desirous to find possible drug candidates but to find compounds that interact with signal transduction pathways, thus providing biochemical probes. Recent work by Obara[7,25] has deepened our understanding of the signal transduction pathways for neurotropin biosynthesis. There is evidence to support multiple pathways that elicit the biosynthesis of neurotrophic factors. In this work it is argued that scabronine G and its methyl ester are selective agonists of Protein Kinase C-ζ. Compounds related structurally to NGF inducing compounds could be used as tools to develop an understanding of neurology on a molecular level.

Synthesis Efforts

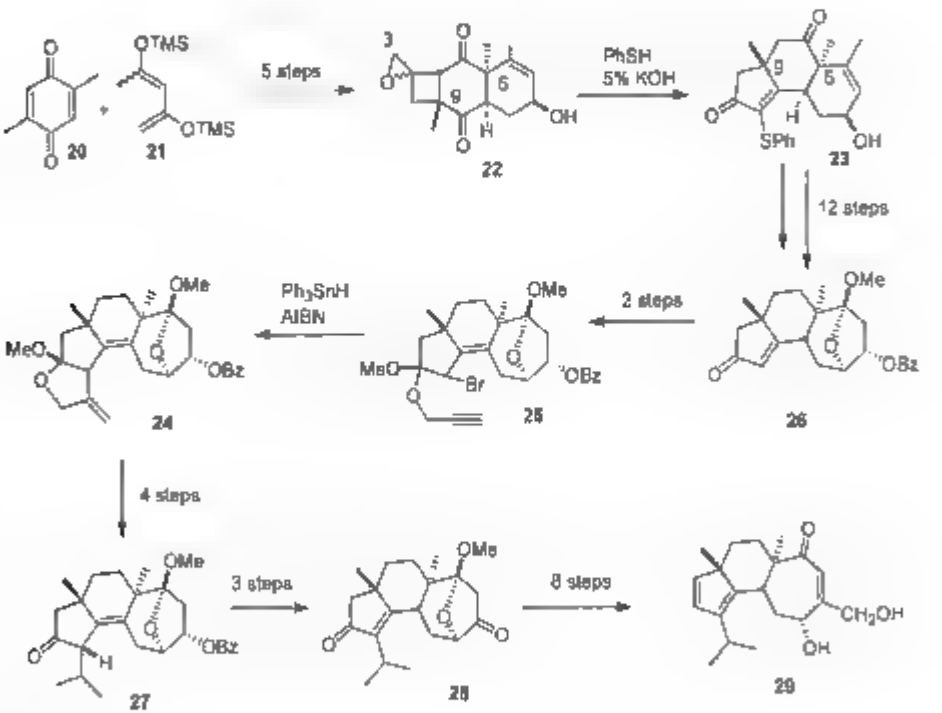
The interesting biological activity and unique chemical structure of the cyathanes have made them attractive targets for total synthesis. A review of the synthetic chemistry targeting the cyathanes has recently been published.[26] Since that time there have been four publications that describe a synthetic approach to a cyathane target. This section contains a condensed version of the previously published review and combines with it the recently published work. There have been a total of nine published approaches to different cyathanes (not including this one). Four of those approaches resulted in a total synthesis.

Total Synthesis

All of the total syntheses are racemic. Allocyathin B_2 has been synthesized twice. This target does not require a solution to the formation of the *trans* B-C ring fusion, because of the sp^2 center at C5. There has been one synthesis of allocyathin B_3 and another of sarcodonin G. Each of these compounds contains the *trans* 6-7 ring fusion, and sarcodonin G has an additional stereogenic center at C18.

Ayer and Ward[27,28] published the first synthetic approach to the cyathanes. Recently, Ward[29] expanded this work to include the total synthesis of allocyathin B_3. The synthesis relies on two key cycloaddition reactions to form the polycyclic ring system. This synthesis is one of two that correctly sets the *trans* 6-7 ring fusion.

The synthesis begins with a Diels-Alder reaction between the benzoquinone **20** and the diene **21** (Scheme 4). The product is subjected to a [2+2] cycloaddition reaction with ketene followed by functional group manipulation and epoxidation, providing the key



Scheme 4

intermediate **22**. The correct relative configuration between the stereogenic centers at C9 and C6 is set by the two consecutive cycloaddition reactions. The cyclopentenone is then formed by reaction of **22** with thiophenylate to provide the tricyclic compound **23**. The

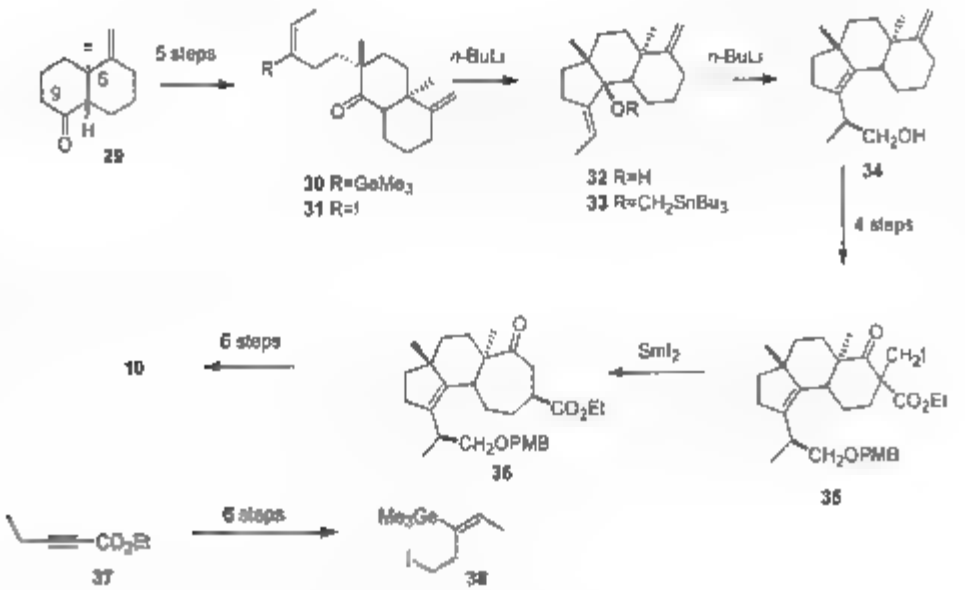
intermediate **23** is formed by opening of the epoxide at the least hindered position with thiophenylate, followed by a retro-aldol reaction. An aldol reaction between the α carbon of the newly formed carbonyl and the ketone at C4 forms the cyclopentenone. Several functional group manipulations are then necessary. The C-ring is formed by oxidative cleavage of the cyclohexenol ring followed by aldol condensation to provide the intermediate **26**, which has all four key stereogenic centers set correctly. The overall yield of **26** from benzoquinone **20** is ~10%.

The final steps of the synthesis install the isopropyl group at C3 by radical cyclization of the mixed ketal **25**. The desired stereochemistry at the B-C ring fusion is lost prior to cyclization. Opening of the ketal and removal of a hydroxyl group provides the ketone **27**. Selective reintroduction of the stereogenic center at C5 is possible, because of the control exerted by the oxygen bridging the 7 membered carbocyclic ring in the diketone **28**. Several functional group manipulations and the addition of one carbon atom are necessary to complete the synthesis of allocyathin B_3 (**29**).

Piers and coworkers[30] recently reported the synthesis of sarcodonin G (**10**). This is the only synthesis besides Ward's that provides a compound with the *trans* 6-7 ring fusion. In addition, the hydroxyl group at C19 makes C18 a stereogenic center.

The strategy is based on the use of the decalone **29** as a B-C ring precursor (Scheme 5). The thermodynamic stability of the *trans* decalone is used to obtain the desired stereochemistry at what will become the B-C ring junction. The stereogenic center at C9 is introduced in a controlled manner by the order of addition of electrophiles to the enolate of ketone **29**. The iodo vinyl germane **38** is the key electrophile and its preparation requires the largest number of linear steps from **29** to **30**. Conversion of **30**

into the vinyl iodide **31** precedes lithium-halogen exchange, which results in intramolecular addition to the carbonyl to provide the alcohol, **32**. Formation of the methyl stannyl ether **33** occurs easily. The key [2,3] sigmatropic rearrangement following the Still-Mitra protocol[3] provides the alcohol **34**. This reaction introduces a double bond between C3 and C4 and the desired stereochemistry at C18.

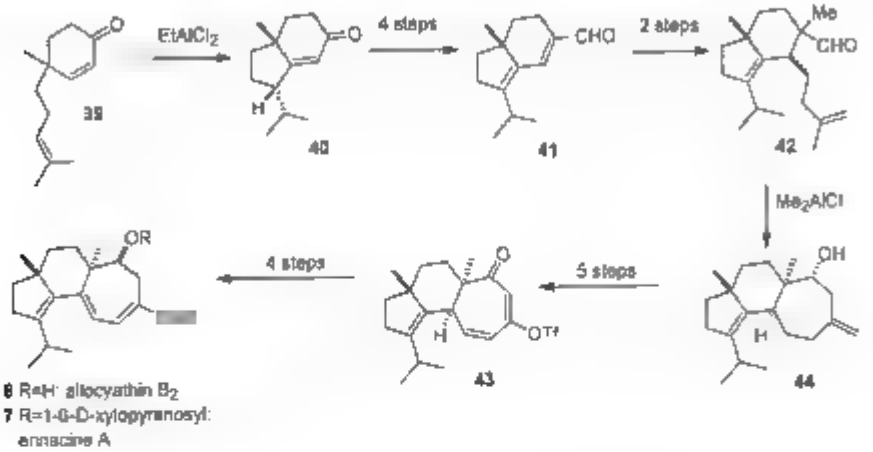


Scheme 5

In order to form the 7-membered C-ring, **34** is converted into the ketone **35**. Ring expansion is triggered upon exposure to SmI_2 to give the ketone **36**. The ketone **36** contains all the correct stereogenic centers in the entire cyathane system, but several more steps are needed to complete the total synthesis.

Snider and coworkers[32,33] were the first to report the total synthesis of a cyathin and the only group to report the synthesis of an erinacine. The synthesis is racemic, but glycosidation of synthetic allocyathin B_2 (**6**) provides (+)-erinacine A (**7**). The discovery

of a synthesis of the bicyclic ketone **40** was made while exploring the conjugate addition of alkenes to unsaturated carbonyl compounds (Scheme 6).[44] It was recognized that this compound could be a useful starting point for a total synthesis of a cyathane



Scheme 6

The enone **40** was converted into the conjugated dienal **41** using standard chemistry. Conjugate 1,4-addition of an alkyl cuprate followed by alkylation gives the aldehyde **42**. The conjugate addition resulted in the incorrect stereochemistry at C5, but alkylation was selective for the desired stereochemistry at C6. The ring system of the cyathanes is then formed via a carbonyl-ene reaction catalyzed by Me_2AlCl, providing alcohol **44**, which contains all **20** carbons of the diterpenes, as well as the desired relative stereochemistry at C9 and C6. Removal of C15 is necessary in order to introduce the correct oxidation states in the C ring. The reintroduction of C15 is effected by carbomethoxylation of the enol triflate **43**.

The undesired *cis* fused B-C ring junction is obtained during this synthesis. Unable to prepare the correct relative stereochemistry, Snider and coworkers converted the

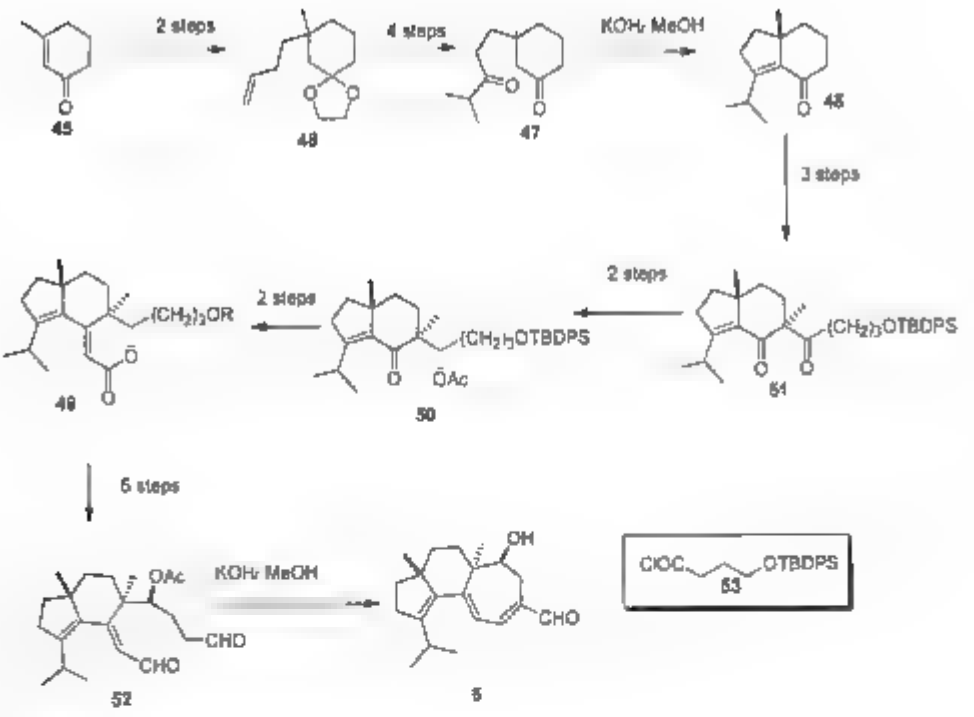
stereogenic center at C5 to a sp^2 hybridized carbon, following the same general procedures used by Ayer [2] in his structural elucidation studies, providing allocyathin B_2 (**6**). Glycosidation with 2,3,4–tri-O-acetyl-α-D-xylopyranosyl bromide, followed by acetate hydrolysis provides (+)-erinacine A (**7**) and its diastereomer as a separable 1:1 mixture.

Tori and co-workers[35] disclosed a total synthesis of allocyathin B_2 shortly after Snider's report. Their strategy centered upon the application of two key aldol cyclizations to annulate both rings A and C onto a B ring precursor. Cyclization of the 7-membered C ring was targeted late in the synthesis.

The synthesis begins with the copper catalyzed conjugate addition of butenyl Grignard to methyl cyclohexenone **45** (Scheme 7), followed by protection of the ketone as an ethylene glycol ketal to provide **46**. Oxidative cleavage of the olefin, addition of isopropyl Grignard to the resulting aldehyde, oxidation and finally removal of the ketal provides the diketone **47**. Aldol cyclization in methanolic potassium hydroxide forms the bicyclic enone **48**. This compound contains the A-B ring system and one stereogenic center at C9.

Acylation of the kinetic enolate of **48** with the acid chloride **53** gives a mixture of O and C acylated products as well as recovered starting material. Recycling of the undesired materials is necessary. Alkyation of the diketone under basic conditions with methyl iodide introduces the methyl group at C6 with the desired stereochemistry forming compound **51**.

Selective reduction of the diketone with $Zn(BH_4)_2$ and acylation provides the acetate **50**. This is the precursor needed for the formation of a critical carbon-carbon



Scheme 7

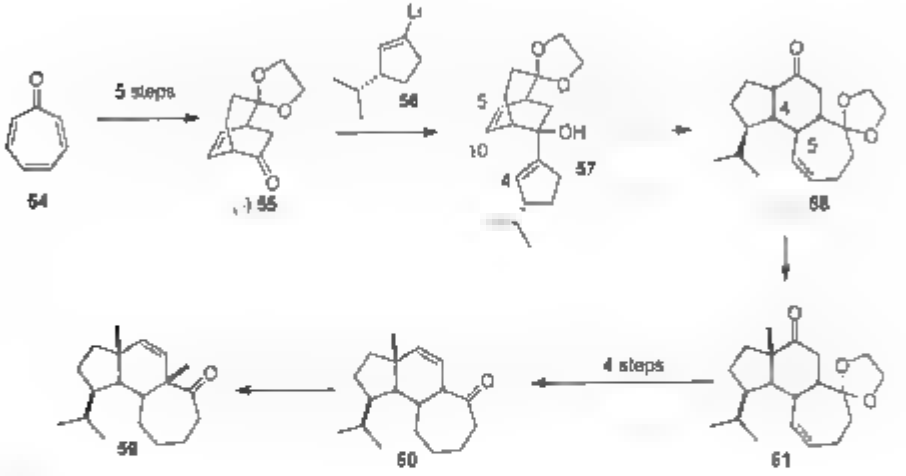
bond by a crossed intramolecular aldol reaction. Intramolecular aldol reaction followed by elimination of the β-hydroxyl group with $SOCl_2$ in pyridine provides the tricyclic lactone **49**. Reduction of the lactone with LAH provides an intermediate triol that is carried through several protection-deprotection sequences and oxidations to give the dialdehyde **52**. The dialdehyde **52** then undergoes aldol reaction to provide allocyathin B_2 (**6**) directly.

Partial Synthesis

The cyathanes have inspired many synthetic investigations that did not result in a total synthesis. All of these approaches have been published within the last decade and are either currently incomplete or abandoned due to unexpected difficulties. Many of the approaches are non-racemic.

Paquette and coworkers[36] disclosed an early approach to the cyathanes. This approach relied on a key sigmatropic rearrangement process to form the C4-C5 bond of the cyathanes. This study succeeded in rapidly assembling a non-racemic 5-6-7 tricyclic system, however, attempts to introduce the *anti* 1,4-methyl groups were unsuccessful.

Construction of the carbocyclic system begins with tropone **54** (Scheme 7). After



Scheme 8

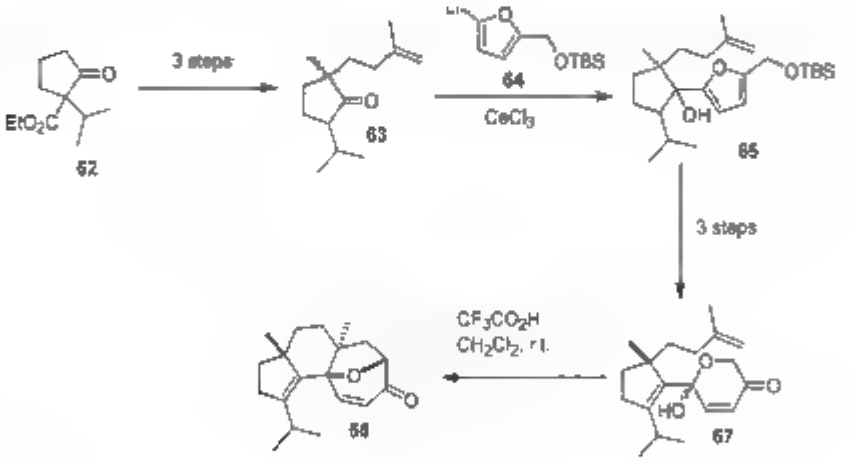
cycloaddition, functional group manipulation, and resolution the non-racemic ketone (-) **55** is obtained. Addition of the homo-chiral organolithium reagent **56** gives the key intermediate **57**. Sigmatropic rearrangement is triggered using KH and a crown ether to give the tricylic compound **58**. This compound contains the carbocyclic skeleton of the cyathanes in non-racemic form but lacks key carbon-carbon bonds at stereogenic centers. Alkylation of the thermodynamic enolate of **58** provides **61** selectively.

Attempts to introduce the desired *anti* 1,4-methyl groups were unsuccessful. A single methyl group could be readily introduced selectively at C9; however, all other attempts to introduce the desired methyl group with the correct stereochemistry at C6

failed. As an example, ketone **60** was prepared from **61**. Alkylation of the enolate of this ketone provided the unwanted compound **59**, which has the incorrect stereochemistry at C6.

Magnus and co-workers[37] have reported a synthesis of the racemic cyathane skeleton. This approach succeeds in a rapid and stereoselective synthesis of the 5-6-7 ring system with the desired *anti* 1,4-methyl groups. The key step in the synthesis is a pyrylium ylide-alkene [5+2] cycloaddition.

The synthesis begins with keto-ester **62**, which is readily prepared from diethyl adipate (Scheme 9). Keto-ester **62** is submitted to alkylation and decarboxylation steps to

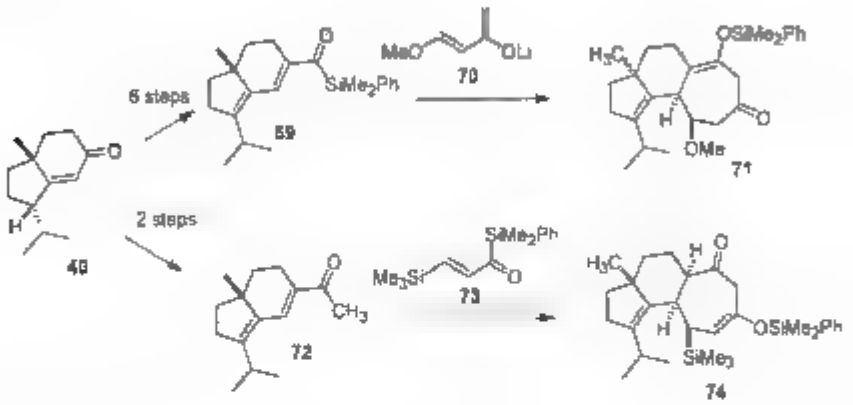


Scheme 9

give the ketone **63**. Addition of the cerate derived from lithio furan **64** gives the alcohol **65** as a mixture of stereoisomers. Dehydration of the alcohol and oxidative opening of the furan provides the pyranone **67**. Treatment of this compound with trifluoroacetic acid at ambient temperature gives the tricyclic oxo-bridged enone **66**. No further work with this approach has been reported.

Recently Takeda and coworkers[38] have disclosed their own racemic approach to the cyathanes. Two different methods of forming the cyathane C ring were explored Each of these methods uses a key Brook rearrangement initiated [3+4] annulation

In one approach the intermediate **40**, also used by Snider, is transformed into acyl silane **69** and treated with the lithium enolate **70** (Scheme 10) The final product, formed

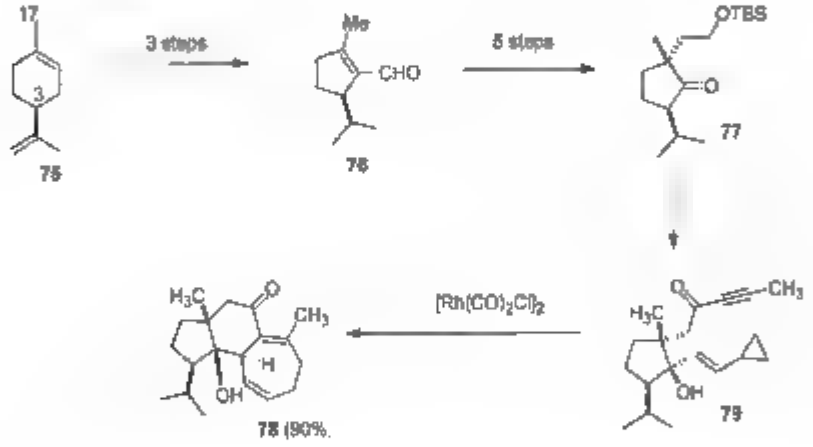


Scheme 10

from a Brook rearrangement, is the tricyclic compound **71** The incorrect stereochemistry is obtained at C5 and an epimeric mixture is obtained at C9 In the other approach the A B ring precursor **40** is converted into methyl ketone **72**. Generation of the lithium enolate of **72** and treatment with the acyl silane **73** gives the tricylic compound **74** In this case the center at C9 is set correctly, yet again the stereogenic center at C5 is incorrect. The late stage intermediate **74** contains the carbocyclic framework of the cyathanes, but lacks either the angular methyl group at C6 or the *trans* B-C ring fusion

The Wender group[39] has a reported a non-racemic synthesis of the carbocylic skeleton of the cyathanes. The approach uses a novel intramolecular [5+2] cycloaddition to construct the B and C rings simultaneously

The synthesis commences from the chiral material (−)-limonene (75) (Scheme 11) The conjugated enaldehyde **76** is constructed by selective hydrogenation, oxidative cleavage of the alkene and aldol reaction of the resulting dicarbonyl compound. After conjugate addition of a two carbon unit and subsequent functional group manipulations the ketone **77** is obtained. Addition of the needed carbon fragments to **77** and adjustment of the functional groups provides the cyclization precursor **79**. Reaction of **79** with a rhodium(I) catalyst in 1,2-dichloroethane provides the tricyclic compound **78** is good yield and excellent purity



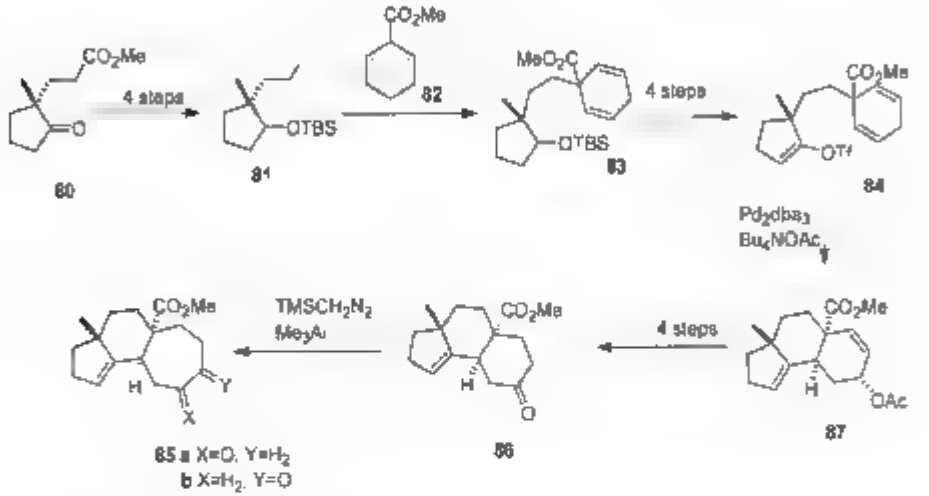
Scheme 11

This approach constructs the carbocylic skeleton rapidly and in non-racemic form, but only one of the three key stereogenic centers are established. In addition, the methyl group at C14 is not desired.

The latest synthetic effort to be published relating to the cyathanes was a model study reported by Desmaele and coworkers.[40] This approach is non-racemic and uses a

Heck reaction to close the C ring of the cyathanes as a 6-membered ring. This ring is then expanded using diazomethane chemistry

The study uses chiral keto-ester (*R*)-**80** as the starting material. Several functional group manipulations are used to provide the iodide **81** (Scheme 12). This material is then used to alkylate the enolate of the unconjugated diene-ester **82**, providing the



Scheme 12

intermediate **83**. After more functional group transformations the vinyl triflate **84** is prepared. The optimum conditions necessary for the Pd catalyzed cyclization reaction were determined, which give the allylic acetate **87** in good yield and high selectivity. After acetate hydrolysis a series of reactions isomerize the allylic alcohol to the saturated ketone **86**. The second key step is ring expansion of **86**. In this case a mixture of expansion products **85a, b** is obtained.

The model study demonstrates that the cyathane carbocyclic system can be made using this strategy. Besides the problem with the selectivity of the ring expansion step, the stereogenic center at C5 is set incorrectly. Desmaele argues that more highly

functionalized compounds would be expected to give higher selectivity in the ring expansion step.

Oxidative Cyclizations

Our two-step strategy requires the conjugate addition of an organomagnesium compound to an α, β-unsaturated enone with formation of the silyl enolether. The product of this reaction is then oxidized in an electrochemical cell. The use of carbon centered radicals or cations in synthetic chemistry is well documented and treated theoretically. The use of radical-cations in synthetic chemistry is less well documented and less understood. Radical-cations can be generated by the oxidation of electron rich alkenes. If a molecule has two electron rich double bonds, then bond formation can occur *via* oxidation intramolecularly.

This section provides background information on the development of this method. A non-inclusive discussion of both chemical and electrochemical oxidation reactions, specifically those that result in intramolecular bond formation between two or more nucleophilic carbon atoms, comprises this section of Chapter 2.

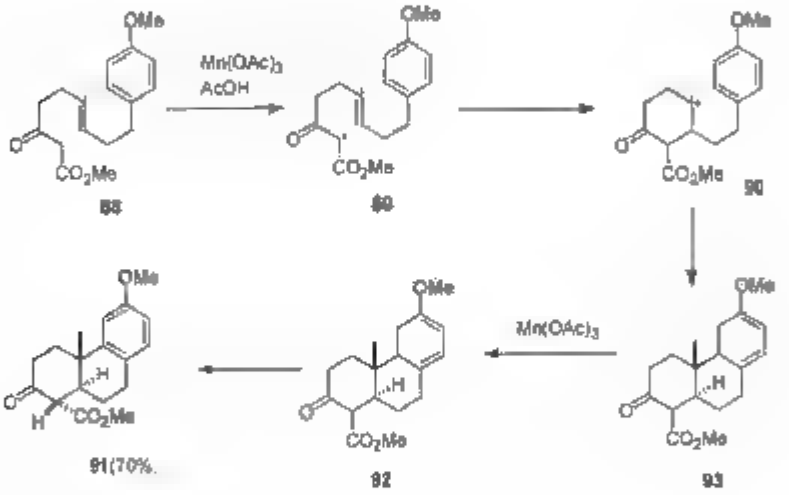
Chemical oxidation

The reaction of an organic substrate with a metallic reagent is standard practice and a familiar technique to most organic chemists. There is considerable interest in using metal mediated oxidations of organic substrates to form carbon-carbon bonds. A useful place to begin the discussion is with the synthetic utility of $Mn(OAc)_3$ in the oxidation of β-dicarbonyl compounds, because these reagents have been well studied synthetically[3] and provide the same bond disconnections as in our own work.

The oxidation of β-dicarbonyl compounds with $Mn(OAc)_3$ is expected to result in the formation of an α-carbonyl radical, which can react with a suitably oriented alkene,

alkyne or arene. The initial oxidation occurs from the manganese enolate of the carbonyl and the resulting radical can be either free or bound to manganese. The termination step of the radical chain reactions can vary. The synthetic utility of $Mn(OAc)_3$ alone is rather limited, being restricted to α-substituted β-dicarbonyls and reactions that cause cyclization into an arene.

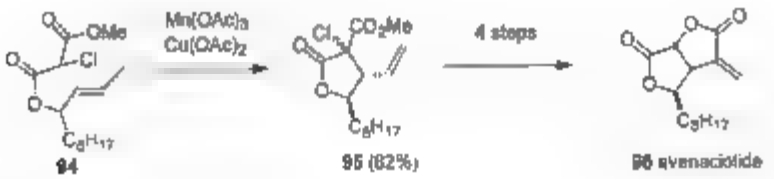
A double cyclization occurs when **88** is reacted with two equivalents of $Mn(OAc)_3$ (Scheme 13).[42] The radical **89** probably undergoes 6-endo cyclization to give the alkyl



Scheme 13

radical **90**. This radical then adds to the aromatic ring. The resulting radical is then readily oxidized to the cation **92**, which rearomatizes to give the product **91** stereoselectively and in good chemical yield. The ease of oxidation of the radical **93** is the most likely reason why the reaction proceeds well. Typically, products that still contain an α- proton undergo further oxidation, thus lowering the yield. Additionally, if more electron ring aromatic rings are employed in reactions similar to that of **88** the yields are lowered due to product oxidation.

One method to overcome product oxidation in these reactions was developed in the labs of Barry Snider.[43] In this method the β-dicarbonyl compound is further substituted by a chlorine atom. This prevents over-oxidation of the product, and reductive removal of the chlorine can be used to give the unsubstituted product in a good two-step yield. Copper(II) acetate is used to oxidatively terminate the radical. The chlorine atom can also be synthetically useful in further operations. The cyclization of **94** provides a mixture of epimers **95** in good yield (Scheme 14). The ring forms selectively

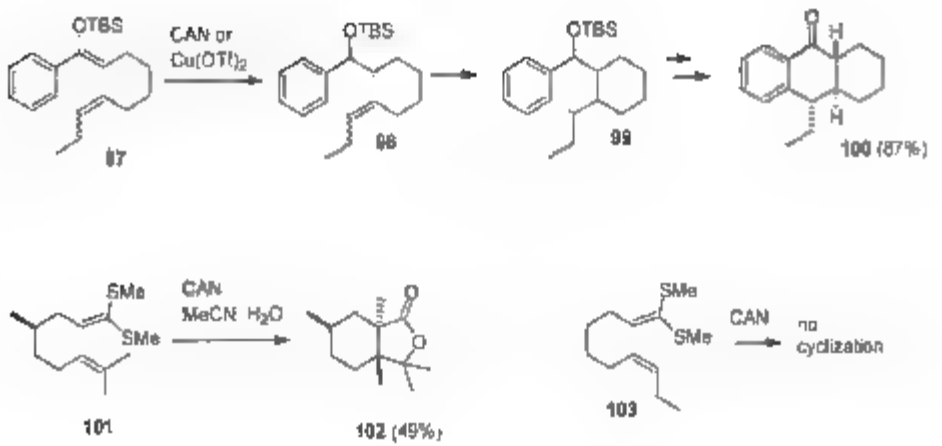


Scheme 14

with the substituents *trans*. The chlorine atom causes the carbon bound to it to be electrophilic, and this serves a useful purpose in the synthesis of avenaciolide (**96**).

The oxidation of both alkyl and silyl enolethers as well as dithioketene acetals has been studied using copper(II) and cerium(IV) reagents.[44-46] These reactions are mechanistically different from the oxidation of β-dicarbonyl compounds with manganese(III). The question of when oxidation and cyclization steps occur and the nature of the intermediate species is only partially answered.

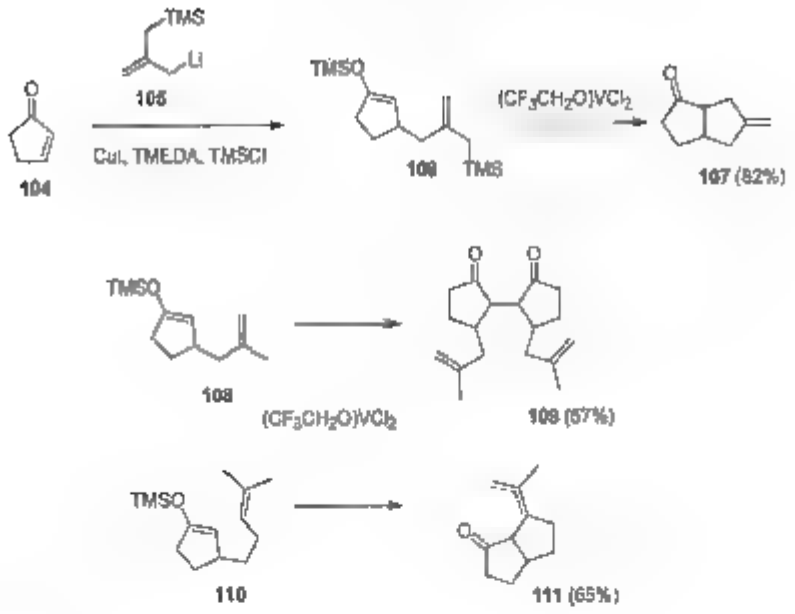
The oxidation of substrate **97** gives rise to a radical cation intermediate, which then cyclizes (Scheme 15). The timing of the second cyclization, oxidation and the loss of the



Scheme 15

silyl group to give **100** is in question. The intermediacy of the radical cation **99** has not been firmly established. Other electron rich alkenes can be oxidized using the same general method. Dithioketene acetals were found to oxidize under the same conditions. In this case, water is present to trap the cation or radical cation intermediate and give the lactone **102** when **101** is oxidized. The radical-cation generated from oxidation of the dithioketene acetal is less electrophilic than the one generated from a silyl enolether. This is demonstrated by the fact that no cyclization products are observed in the oxidation of **103**.

A two-step synthetic method to form polycyclic ring systems was recently reported by Livinghouse.[47] This method relies on the conjugate addition of a cuprate derived from the lithio allyl silane **105** to the enone **104**, providing the silyl enol ether **106** (Scheme 16). A vanadium(III) reagent oxidizes the bifunctional compound to the cyclic unsaturated ketone **107**. In this case the enol ether oxidizes and the allyl silane functions as a nucleophile. The reaction must proceed through an unfavorable 5-endo ring closure. When the alkene **108** is oxidized under the same conditions only dimerized product **109**



Scheme 16

is observed. The alkene **110** cyclizes cleanly in a 5-exo manner, providing the cyclic unsaturated ketones **111**

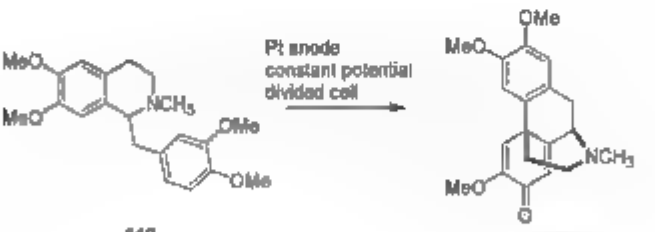
Anodic oxidation

Organic electrochemistry is different from the techniques usually applied in synthetic organic chemistry experiments. A review on synthetic applications of anodic electrochemistry has recently been published.[48] Unlike chemical oxidations, oxidations of organic substrates using electrochemistry are less familiar to the organic chemist. It is beyond the scope of this manuscript to rigorously treat organic electrochemistry theoretically, but some general concepts are provided.

An electrochemical reaction is performed by applying a potential difference across a conducting solution. A conducting solution must necessarily contain substances that can be oxidized and reduced. Reaction of the substrate occurs when the molecule enters

an electric field strong enough to cause electron transfer between the electrode and the substrate. This only occurs close to the electrode surface, within a few molecular diameters. Organic electrochemistry can be performed in a variety of solvent-electrolyte systems. A dissociated salt is needed as an electrolyte in order to preserve charge balance when the neutral organic molecule becomes ionized. A very polar solvent is typically needed in order to dissolve the salt. Electrochemical reactions can be performed in divided cells, where the anodic and cathodic reactions are separated by an ion permeable membrane or they can be performed in an undivided cell. Reactions are performed either under constant current or constant potential control.[49]

The intramolecular oxidative couplings of aromatic rings[50] are the oldest and most well known examples of synthetic organic electrochemistry. As an example, controlled potential electrolysis of the diaryl amine **112** leads to the morphinandienone **113** (Scheme 17).

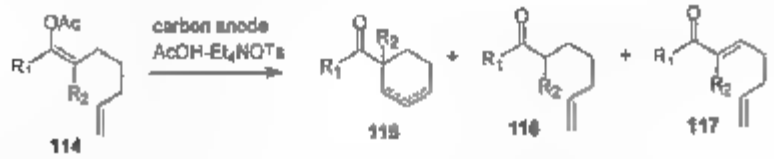


112 **113** (54%)

Scheme 17

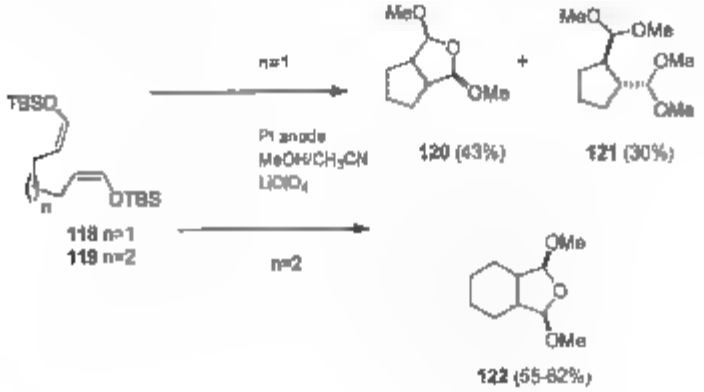
Other anodic reactions where electron rich double bonds are coupled intramolecularly have been discovered and developed. Shono and coworkers[51] were the first to report the anodic oxidation of an enolether in order to initiate cyclization. When the diene **114** is oxidized the major products are the isomeric cyclohexenes **115** and the

hydrolysis products **116** (Scheme 18). The electrochemical cell was undivided and utilized simple carbon electrodes under constant current conditions. The conjugated enone **117** is a minor product in some cases.



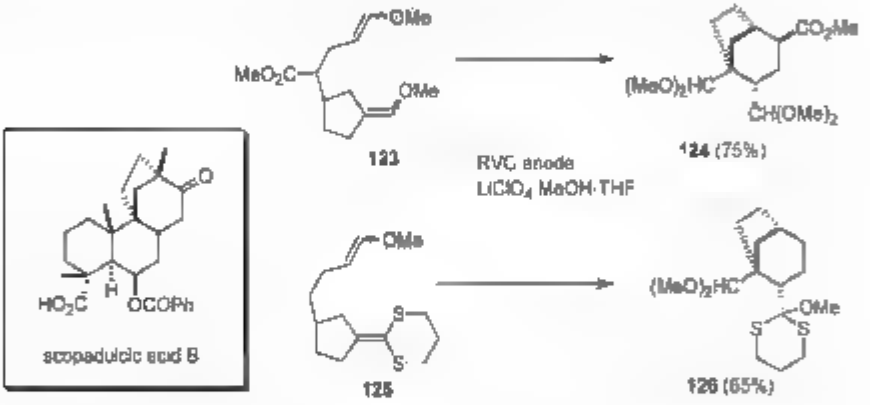
Scheme 18

The laboratory of Kevin Moeller[48,52-55] has recently investigated the oxidative cyclizations of electron rich olefins electrochemically. The first reports were of bis-enolether substrates. Productive cyclizations were shown to occur, forming cyclohexanes and pentanes, when the substrates **118** or **119** were oxidized (Scheme 19). Though the selectivity of the reaction was low, the overall chemical yield was good. Several other coupling reactions of different electron rich olefins have been described, including allyl silanes and styrenes.



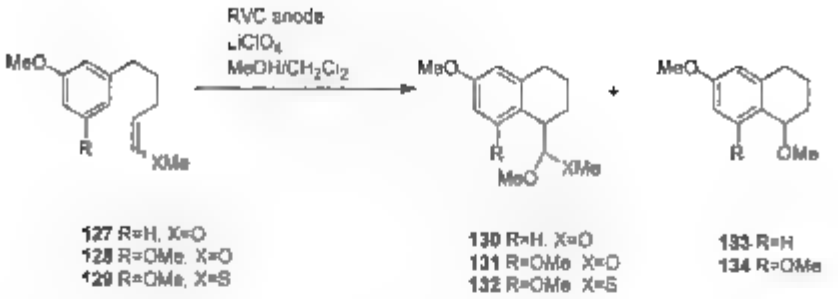
Scheme 19

A study aimed at the synthesis of scopadulcic acid[52,58,59] demonstrated that intramolecular oxidative cyclizations could be useful in synthetic efforts. Methods were found to enforce stereoselectivity and differentiate between the two carbon atoms left in carbonyl oxidation states. A high chemical yield and good stereoselectivity was observed in the formation of the [3.2.1] octane **124** by the anodic oxidation of **123** (Scheme 20). Moeller found that differentiation of the two dimethoxy acetals was impossible; therefore, use of a dithioketene acetal in the reaction was explored. The thioorthoester **126** was obtained in good yield with high stereoselectivity from the precursor **125**.



Scheme 20

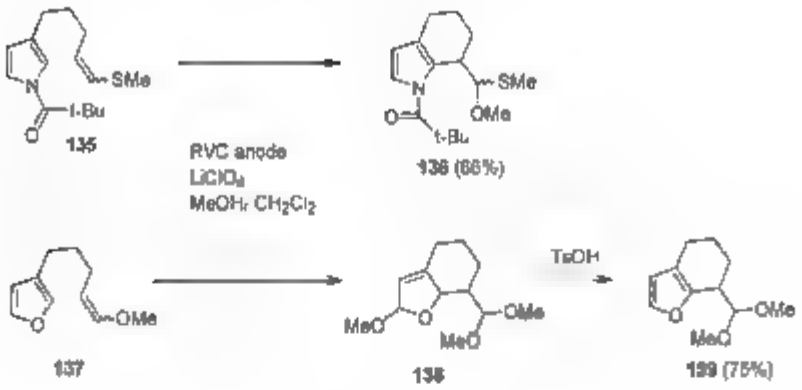
The anodic coupling of aromatic rings and other electron rich olefins has also been explored.[57] Anodic oxidation of suitable arene substituted enolethers led to cyclization products. Problems were encountered when oxidation of the cyclized product was competitive with the oxidation of starting material. The over-oxidized products **133** and **134** were obtained as a large percentage of the mass when **127** or **128** were subjected to constant current electrolysis (Scheme 21). A controlled potential electrolysis led to a



Scheme 21

more selective formation of **130** from **127**. however, controlled potential conditions were discovered not to be synthetically useful. The desire to minimize over-oxidation led to the use of the vinyl sulfide **129** as a substrate for constant current electrolysis. The cyclized product **132** was obtained exclusively in 72% yield when the substrate **129** was oxidized. Because a vinyl sulfide has a lower oxidation potential than an enolether Moeller argues that the observed selectivity in the reaction of **129** as compared to **128** is due to a larger difference in the oxidation potential of products relative to starting materials.

Anodic oxidation of the vinyl sulfide-pyrrole **135** under constant current conditions led to a good yield of the cyclized product **136** (Scheme 22). An enolether was found to be a suitable coupling partner when furan **137** was oxidized in a similar manner. The high yields of the furan **139** were attributed to the intermediacy of the compound **138**. Dihydrofuryl acetals such as **138** have a much higher oxidation potential than the starting material. Examples where 7- and 8-membered rings were formed from the oxidation of furyl substituted alkyl enolethers have been reported, although in modest yields



Scheme 21

Conclusions

The cyathanes have inspired many attempts at their synthesis. All of the known synthetic approaches and the reasons why these natural products are attractive targets were given first. This is to provide a comparison to the strategy that we employ in our synthetic approach. A discussion of specific methods of forming carbon-carbon bonds was also discussed in this chapter. This is to provide background information on the development of the key synthetic operation in our approach to the cyathanes.

CHAPTER 3
RESULTS AND DISCUSSION

This chapter reports our investigations into the application of a new method in a target oriented synthesis. The first section of this chapter provides the results and gives a discussion of our study of the electrochemical oxidation of furyl substituted silyl enolethers. The last section provides the results of a synthetic approach to the cyathanes using this oxidation reaction as a key transformation.

New Two Step Annulation Strategy

The furan ring has frequently been exploited in synthetic chemistry, because it can be easily transformed into a diverse range of structures and functional groups.[61] Recent examples where the furan has been used as a synthon include the synthesis of macrolides,[6] sugars[62], and vitamin D analogues.[63] Our interest in developing a method to form fused polycyclic furans is due to a desire to synthesize natural terpenes and alkaloids.[64] The wide range of synthetic equivalencies of furan makes this heterocyclic system a useful synthon. Many different polycyclic systems could be synthesized if a method of synthesizing polycyclic furans can be developed. One could argue that this method could find application in the combinatorial or high-throughput screening of terpene or alkaloid like compounds as drug substances,[65] as well as a key step in a target oriented synthesis.

We report here a new two step method to construct polycyclic furans. Conjugate addition of a furan fragment **141** to an α,β-unsatutrated enone **140** in the presence of TMSCl gives the silyl enolether **142** (Scheme 23). Oxidation of this substrate in an

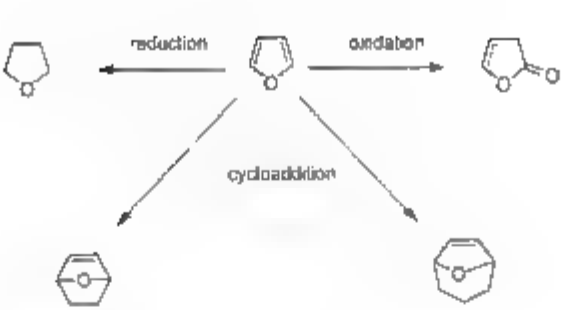
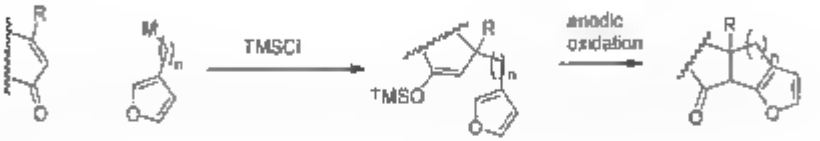


Figure 2 Some synthetic equivalencies of furan.

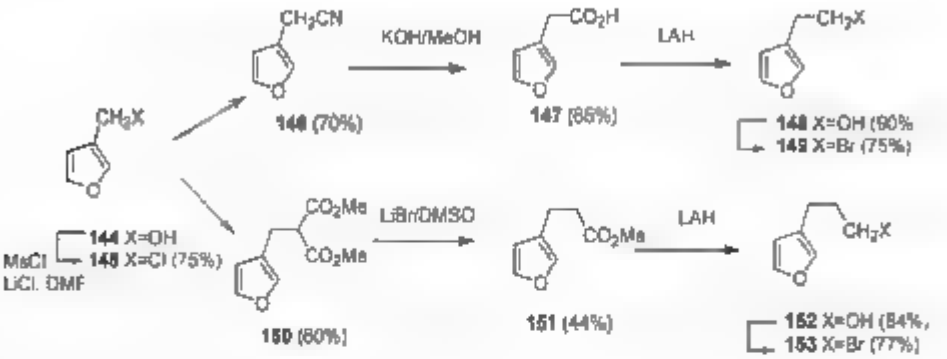


Scheme 23

electrochemical cell provides the fused tricyclic furan **143**. The precedent for the development of this method comes from the labs of Kevin Moeller.[53] His work demonstrated that furan could be coupled oxidatively to alkyl enolethers. Other furan-olefin oxidative couplings have not been reported. The generation of a silyl enolether from a conjugate addition reaction is well known.[46,47] A similar two-step method was reported by Livinghouse,[47] which used a cuprate addition-silylation reaction to provide silyl enolethers as substrates for vanadium mediated oxidations.

Most of the enones **140** used in this study are commercially available. The 3 substituted furan **141** must be synthesized. Our first task was to synthesize useful quantities of these materials in order to begin our studies. A survey of the literature offered several possibilities.

The simplest way to prepare the requisite alcohols appeared to be by elaboration of furan methanol **144** [65] Following literature procedures, alcohol **144** is first converted to the chloride **145** (Scheme 24). The chloride **145** is then reacted with a suitable



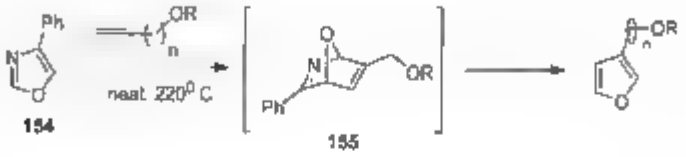
Scheme 24

nucleophile To prepare furan ethanol **148**, the chloride **145** is reacted with sodium cyanide to give nitrile **146**. The nitrile **146** is then hydrolyzed to the acid **147** The acid **147** is then reduced with LAH to the alcohol. To prepare the one carbon homologue, the chloride **145** is reacted with dimethyl malonate sodium salt. Decarboxylation of the malonate **150** to the methyl ester **152** is accomplished by heating in DMSO with LiBr Finally, the alcohol **153** is prepared by reduction with LAH

These steps were repeated following published procedures, and in most cases the yields were close to those reported. We found that purification was not necessary throughout the entire procedure The alcohols were purified prior to conversion into the alkyl bromides We followed these routes to prepare the alcohols initially, but the expense of the starting furan methanol **144** and the difficulty associated with procuring a regular supply caused this route to be abandoned Of all the methods available to convert

alcohols to alkyl bromides, tosylation and displacement of the tosylate with LiBr in acetone was the most convenient, providing nearly pure material in high yields

The preparation of 3-substituted furans by the reaction of an alkyne and oxazole **154** has also been reported (Scheme 25).[69] This method relies on a Diels-Alder reaction

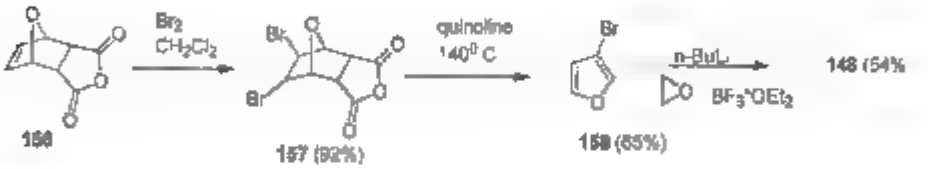


Scheme 25

between the diene system in **154** and an unactivated alkyne. The intermediate adduct **155** then undergoes a retro Diels-Alder reaction to give the furan product and an equivalent of benzonitrile. The low dienophilicity of the nitrile is responsible for the irreversibility of the reaction. This method was less labor intensive and less expensive in material than the first route, however, the oxazole **154** had to be synthesized from phenacyl bromide. This step could never be carried out in greater than 35% yield. Also, reaction between the alkyne-ol and phenyl oxazole **154** was inconsistent, typically giving low yields (<30%). Reaction with the alkyne-acetate always gave consistently higher yields, but adding two steps to the synthesis was not desirable. This route was used for the preparation of **152**, but was abandoned in the preparation of the furan ethanol **148**.

The synthesis of furan ethanol **148** from the opening of ethylene oxide by 3-lithiofuran has not been reported. The use of 2-lithiofuran as a nucleophile is well known,[70,7] because of the ease of generating this species by deprotonation of furan. The generation of 3-lithiofuran requires 3-bromofuran (**158**).[72] Even though 3- bromofuran is commercially available, we chose to synthesis it, because of its high cost and easy

preparation [7]. The Diels-Alder adduct of furan and maleic anhydride (**156**) is reacted with bromine to give the dibromide **157** (Scheme 26). Purification steps are not required in the preparation of **156** or **157**, and the preparation of these materials can be carried out easily on a kilogram scale. Bromofuran **158** is then synthesized by heating the dibromide **157** in quinoline. This reaction progresses by dehydrobromination followed by a retro Diels-Alder reaction. Distillation of the volatile 3-bromofuran removes it from the reaction equilibrium.

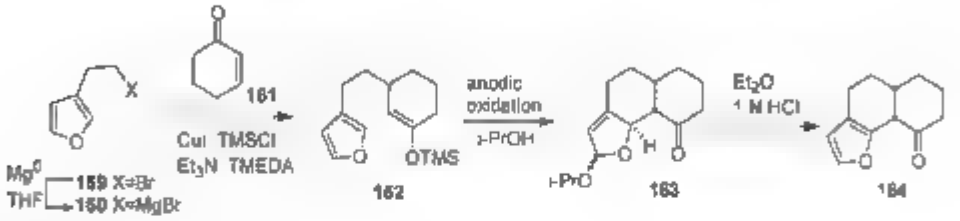


Scheme 26

The generation of 3-lithiofuran is accomplished by treatment of the bromofuran **158** with *n*-BuLi at -78°C. We were surprised to find that 3-lithiofuran would not react with ethylene oxide without an additive. The addition of an equivalent of BF_3•OEt_2 to the reaction mixture resulted in formation of the alcohol; however, great care had to be taken to keep the reaction cold and to quench slowly with bicarbonate, because strong acid would cause decomposition of the furan at higher temperatures.

With a suitable method of preparing material in place, we then turned our attention to the development of the anodic oxidation reaction. The Grignard reagent **159** is reacted with enone **161** to give the silyl enolether **162** (Scheme 27). The electrolysis conditions described by Moeller[52], which utilize acetonitrile-methanol solutions of $LiClO_4$ and 2,6-lutidine, were found to lead to rapid desilylation and formation of the unwanted acyclic saturated ketone. Electrolysis of the enolether **162** in electrolyte solutions containing *n*-

propanol instead of methanol led cleanly to the cyclic furan **164** after workup. An alcohol solvent is required in the electrolysis, because acidic protons must be available for reduction at the counter electrode. The enolether was stable for several days as a dilute solution in these mixtures. The lower nucleophilicity of the more hindered i-propanol can be used to explain why the enolether survives in these solutions.

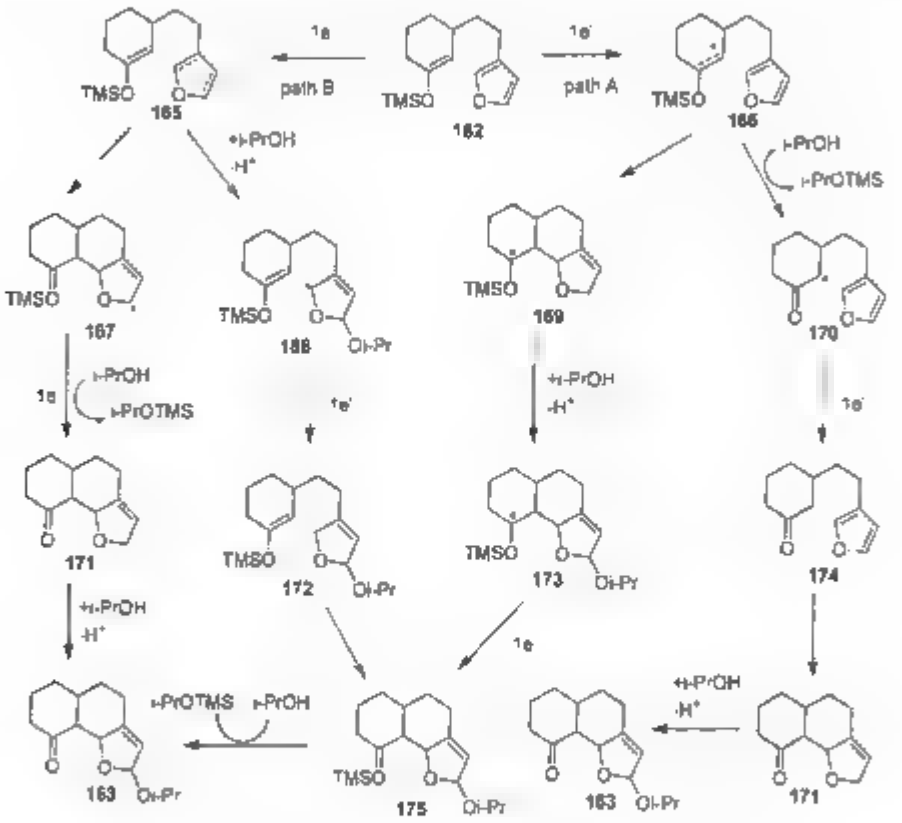


Scheme 27

An attempt was made to understand the reaction on at least an empirical level. We observed that the furan product did not form immediately in the reaction, but only after partitioning of the crude material between ether and aqueous acid. Moeller[52] had reported that dihydrofuran acetals are intermediates in their oxidation studies with furans, and this was argued as a reason why these reactions worked well. When these reactions are monitored, several unstable products are first formed. These products decompose to the furan when treated with acid. We investigated the intermediates by omitting the acidic workup. Two different major compounds could be identified in the NMR spectra. Unfortunately, these compounds could not be purified and were not stable. The NMR spectra of the crude material was resolved enough to make correlation experiments possible. A key assignment was made by observing the long range H-^1H coupling constants[74-76] between protons attached to carbons 2 and 5 in the dihydrofuran ring, which are consistent with two epimeric acetals. This data combined with chemical and

spectroscopic correlations (*vide infra*) allowed us to assign the structure for **163** as shown.

There are two likely mechanistic explanations to account for the observed oxidation reaction (Scheme 28). These two possibilities depend on which functional group is



Scheme 28

undergoing oxidation first and which functional group is serving as a nucleophilic terminator. In path A, the enolether oxidizes first. In path B, the furan ring oxidizes first. Timing of the ring closure, second oxidation, and interaction with solvent is then in question.

If oxidation of the furan ring and ring closure occurs first, then the intermediate **169** would be formed. This intermediate would be attacked by solvent to form **173**. The radical **173** would then be oxidized to the cation **175**, which would interact with solvent, loosing the silyl group to form **163**. Alternatively along path A, the silyl group could be lost first forming the α-keto-radical **170**, which would oxidize to form the cation **174**. Ring closure then forms the intermediate **171**, which would be attacked by solvent to form the product **163**.

If oxidation of the enolether and ring closure occurs first, then the intermediate **167** would be formed. Loss of the silyl group and a second electron would form the intermediate **171**, which would be attacked by solvent to form the product **163**. Alternatively, the radical **168** could be formed after attack of solvent on **165**. A second oxidation would then occur to form the cation **172**, which would be followed by ring closure to give **175**. Loss of the silyl group by attack of solvent would then form the product **163**.

Though none of these pathways can be ruled out, we believe that path A is the most likely (*vide infra*). Cyclization, oxidation and nucleophilic attack of solvent could all occur at different times than those proposed in Scheme 28, but these examples are given as possibilities. To explain the stereoselectivity of the reaction, ring closure could occur in an *exo* like transition state (Figure 3).

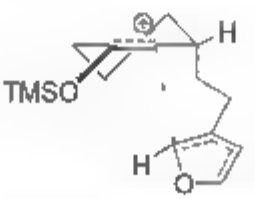


Figure 3. *Exo* like transition state used to explain the stereoselective formation of **163**.

A semi-quantitative study of the anodic oxidation of the enol ether **162** was undertaken. We observed that when reactions were performed quickly by applying a large current, low current efficiency and low yields of product would result. Electrode material also had an effect on the reaction. Only constant current control was used, because reactions under these conditions are generally more synthetically useful and simpler in design. The cell was undivided to insure that any acid formed by oxidation could be neutralized by the lutidine present in solution, and also because this method of cell construction is generally more convenient experimentally.

The data presented in Table 1 demonstrates the effects of current density and electrode material on the yield of product. When carbon is the anode material, the yields

Table 1. Effect of different electrode material and current density in the oxidation of **164**

entry[a]	anode	cathode	current density[b] (mA/cm^2)	yield[c] (%)
1	carbon	steel	0.5	68
2	carbon	steel	1.0	66
3	carbon	steel	5.0	35[d]
4	carbon	steel	10	10[d]
5	carbon	carbon	0.5	67
6	platinum	carbon	0.5	27
7	platinum	carbon	0.1	54
8	RVC	carbon	N.A.	30[d]
9	RVC	carbon	N.A.	35

[a] Reaction conditions: 0.02 M substrate, 0.4 M $LiClO_4$, 0.1 M 2,6-lutidine in a 4:1 acetonitrile:2-propanol solution. All reactions were run under constant current control in an undivided cell. [b] Current density was approximated by dividing the applied current by the surface area of the electrode. [c] Yield is reported for two steps based on the starting enone. [d] The amount of charge consumed was 2.3 times the theoretical 2 F/mol.

begin to fall off sharply when the current density becomes greater than about 1.0 mA/cm^2. The current density could only be a macroscopic parameter affecting the yield. Other parameters that are affected by the changing current density include the overall cell

potential and the rate at which the potential increases. Any of these phenomenons could be affecting the yield.

At a higher current density the concentration of reactive species is very high at the electrode surface. This would increase the likelihood of intermolecular reaction, and since the substrate has two nucleophilic functional groups, higher molecular weight material could form. Also, if the potential of the cell becomes high enough, then oxidation of other components in the mixture could occur, generating species in solution that could react with either of the sensitive functional groups.

Simple graphite anodes functioned best. Platinum could also be used, but the yield of product was more sensitive to current density. Interestingly, reticulated vitreous carbon (RVC) was a poor choice of anode material. Moeller[53] used RVC as the optimum anode material in his furyl substituted alkyl enolether oxidations. We are unable to explain why with our substrate RVC was a poor choice. RVC is a form of glassy carbon with a very high surface area. The choice of cathode material seemed to be irrelevant.

With an optimum electrolysis method in place we explored the reaction of several different cyclic enones in order to understand functional group tolerance and stereoselectivity. Optimization of the conjugate addition reaction was required, though in most cases this reaction was general for different enones and Grignard reagents. The conditions described by Tamis[68] were used to generate the Grignard reagent **159** in a THF solution. When these solutions were titrated the concentrations were found to typically be about 80 % of theory. In practice a 1.3:1.5 molar ratio of alkyl bromide **149** to enone was used, or on smaller scales, titrated solutions of Grignard reagent would be used in slight excess. A mixture of TMSCl/Et$_3$N was used essentially as cosolvent, typically

equal in volume to the amount of THF used as solvent. Copper(I) iodide was used to form the cuprate species from the Grignard reagent.

Several observations were made during the conjugate addition reaction. The 1,2-addition product predominated if the CuI was not purified or if it was not mixed with the Grignard reagent at 0°C prior to cooling to -78°C. Only β-disubstituted enones underwent silylation reactions cleanly without the use of additives. Addition to these enones occured slowly at low temperatures, but rapidly reached completion as the mixture warmed to 0°C. Silylation appeared to occur simultaneously with addition of the cuprate. Enones that were mono-substituted at the β-position would undergo a much faster reaction with the cuprate species, but without the use of additives silylation was incomplete. The addition of TMEDA to the cuprate mixture and a slow warming of the reaction mixture resulted in the clean formation of the silyl enolether.

The silyl enolethers were very hydrolytically unstable and purification attempts were counter productive. Silyl enolethers derived from β-disubstituted enones were more stable. Typical impurities in the crude material were the saturated ketone (derived from cuprate addition without silylation), the 1,2-addition product as well as dimer and oxidation products derived from the Grignard reagent. The formation of the saturated ketone and 1,2-addition product could be eliminated (*vide supra*). Dimer and oxidation products of the Grignard reagent could be minimized by bubbling dry argon through the solvent and could be removed from the crude product by extended drying under vacuum.

The purity of the crude product could be judged by TLC analysis and analysis of the mass balance. All the silyl enolethers characteristically stained in an iodine chamber when the mixtures were analyzed by TLC. The silyl enolethers had large R_f values in

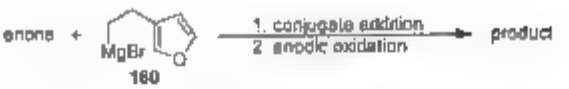
hexane and ethyl acetate or ether mixtures. Some of the enolethers were characterized by NMR, but d_6 benzene or carefully neutralized $CDCl_3$ were required as solvents. Crude yields between 80-95% of theory were typically obtained for nearly homogeneous material.

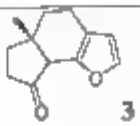
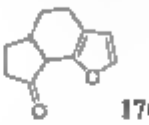
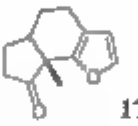
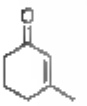
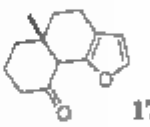
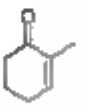
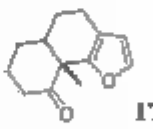
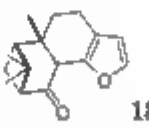
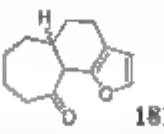
Some simple and readily available enones were reacted under the optimized conjugate addition and anodic oxidation conditions. The reactions were monitored by TLC. In all cases polar intermediates formed that would decompose to the cyclic furans upon partitioning of the crude reaction mixture between aqueous acid and diethyl ether. The *cis* fused ring systems were formed selectively except in the synthesis of **170**, where the *trans* isomer predominated in a 4:1 ratio. This result can be explained by the greater conformational flexibility of the cycloheptyl ring. Another interesting observation is that the strained [3.1.1] system in **169** survives the reaction despite the possible formation of radical or cation-radical intermediates in the vicinity of a cyclobutane.

If the polycyclic furans were not isolated quickly or allowed to stand at room temperature for long in the presence of air, then decomposition would occur. Compounds left standing at room temperature would form an intractable tar within a few days. Coworkers in our group discovered that the α-position between the furan and the carbonyl was susceptible to oxidation. This was discovered when attempts were made to epimerize the ketone **167** with NaOMe in the presence of air. Only the α-hydroxy ketone was obtained.

We turned our attention to a modified strategy, which would allow access to greater structural diversity and test the tolerance of other functional groups to the oxidation

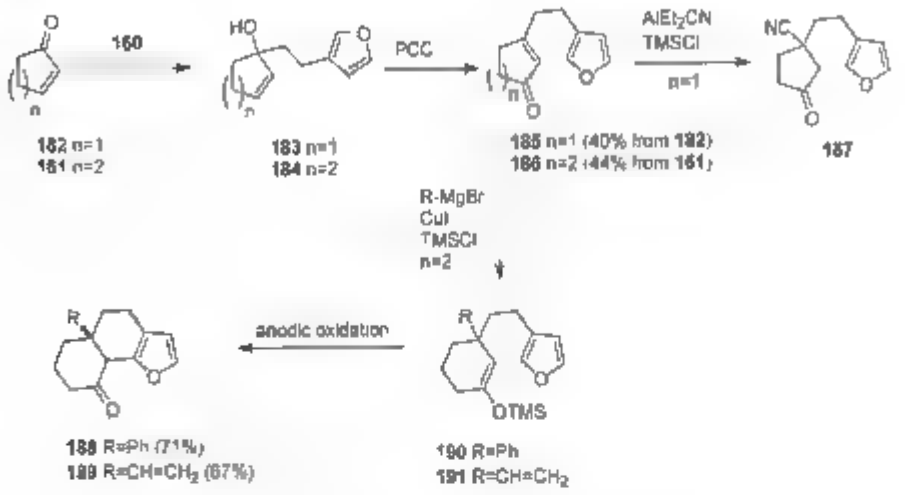
Table 2 Electrochemical Annulation Reactions



entry[a]	enone	product	yield[b] (%)
1		 **3**	78
2		 **176**	64
3		 **177**	64
4		 **178**	76
5		 **179**	65
6		 **180**	69
7		 **181**	58

[a] Reaction conditions: 0.02 M substrate, 0.1 M $LiClO_4$, 0.04 M lutidine in a 4:1 acetonitrile:2-propanol solution. All reactions were run under constant current control with carbon anodes in an undivided cell. [b] Yield is reported for two steps based on the starting enone

reaction. Addition to either enone **182** or **161** of the Grignard reagent **160** led to the allylic alcohols **183** and **184** (Scheme 29). The crude alcohols were then subjected to

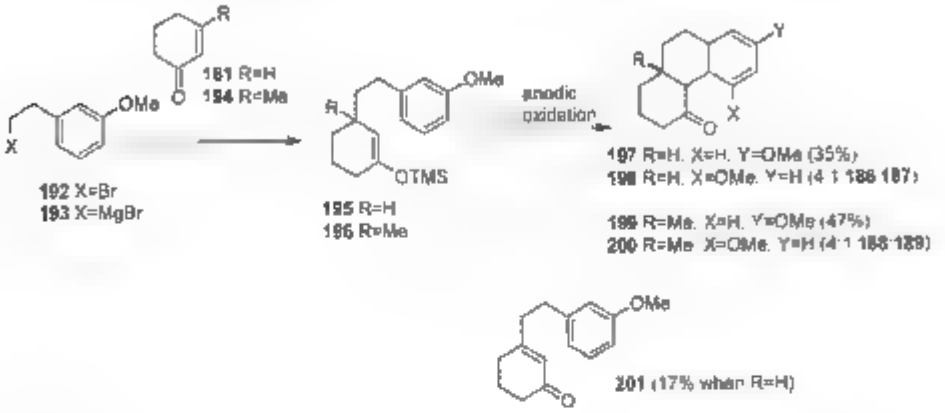


Scheme 29

oxidation with PCC to provide the enones **185** and **186**. Low yields were due in part to 1,4-addition products during the Grignard reaction, and no attempts to optimize the reactions were made. The saturated ketones could easily be separated from the desired enones by chromatography. Reaction of the enone **186** with either vinyl or phenyl cuprate provided the enolethers **190** and **191**. Attempts to add a nitrile group to the enone **174** with Nagata's reagent led to the 1,4-addition product **187**, but we were unable to silylate the enolate *in situ*. Anodic oxidation of silyl enolethers **190** and **191** using the optimized conditions provided the corresponding *cis* fused polycyclic furans **188** and **189** in good yield.

Methoxybenzene substituted silyl enolethers were prepared and oxidized in order to make a comparison between these reactions and the reactions of the furan substituted substrates. The same basic strategy of conjugate addition-silylation was used. Reaction

of the Grignard reagent **193** under our cuprate addition-silylation protocol with either the enone **161** or **194** resulted in the formation of the enolethers **195** and **196** (Scheme 30). The oxidation of these substrates was studied using the same optimized conditions as



Scheme 30

those used in the furan electrolysis. To our surprise, no cyclized product was obtained in the initial studies with enolether **195**. The reaction was characterized by low mass recovery and low current efficiency relative to the consumption of enolether. The only isolatable product was the enone **201**. This compound is likely created by elimination of the β-proton from a cation or cation-radical generated by oxidation of the enol ether.

When the $LiClO_4$ concentration was increased to 1.0 M, cyclization did occur to give **197** and **198** in a low yield. The oxidation of the substituted enolether **196**, which cannot loose a proton, led to a modest increase in the yield of the ketones **199** and **200**. Several non-polar products constituted ca. 20-30% of the recovered mass in these reactions. These products were not characterized. Under these conditions the substrate was consumed with good current efficiency (2.2 F/mol).

The low yield in these reactions can be accounted for in one or two ways. Either the electrophilic radical cation is decomposing before ring closure or the products are being over-oxidized. A combination of the two phenomena could also be occurring and both seem to be equally likely. The nucleophilicity of a methoxybenzene is less than that of a furan.[37] Ring closure is therefore likely to be slower when methoxybenzene substrates are oxidized. This would allow the rate of intermolecular reactions to be competitive with cyclization. The product of the furan oxidation leads to the dihyorofuran acetal, which has a much higher oxidation potential than the substrate. The benzene ring rearomatizes after the cyclization, providing a compound that is likely to have a comparable oxidation potential to the substrate. Why increasing the $LiClO_4$ concentration in the reaction mixture results in cyclization is not easily explained. We used these conditions because a higher concentration of electrolyte lowers the resistance of the electrochemical cell, thus lowering the voltage in a constant current experiment. Yet, the fact the enone **190** is isolated under the non-optimum conditions suggests that oxidation of the substrate is occurring.

All the polycyclic furan and methoxybenzene compounds synthesized were analyzed by four standard NMR techniques. A COSY, GHMBC, GHMQC and NOESY spectrum were obtained for all compounds. The bond connectivity was deduced by observing spin systems in the COSY and one bond C-H correlations in the GHMQC spectra. Up to 3 bond C-H correlations were then made using the GHMBC spectra. The importance of the GHMBC spectra lay in the ability to distinguish protons at the allylic position versus protons α to the carbonyl, since these protons typically had similar chemical shifts. The 2 and 3 bond correlations between these protons and the furan

carbons or the carbony. carbon respectively allowed unambiguous assignments to be made Finally, NOESY spectra were used to determine stereochemistry If protons could not be unambiguously assigned, then a simple derivative was analyzed for stereochemical information.

The determination of the stereochemistry of **164** was done by analysis of the NMR spectra of the L-selectride reduction product Only one alcohol is formed when **164** is treated with L-selectride After assignment of the key carbon and proton peaks, analysis of the NOESY spectrum led to the conclusion that only the *cis* isomer on **164** was formed in the electrolysis reaction Three key NOESY cross peaks are responsible for this conclusion These 3 cross peaks can only be observed simultaneously in the structure as shown in Figure 4 Models show that other isomers may have some conformers which exhibit some of these cross peaks, but not all of these cross peaks would be observed.

Figure 4. Key NOESY crosspeaks observed in the reduction product of **164**

The determination of the stereochemistry of **188** was done by analysis of key NOESY cross peaks. In this case analysis started by observing the NOESY cross peaks of the aromatic protons at δ 7 30 The protons that correlated to the aromatic protons in

the NOESY spectrum must be on the same face of the carbocyclic ring. Since the proton at δ 4.16 correlates to the same protons as the phenyl ring, it was concluded that the bridgehead proton and the phenyl group were *cis* to one another. Another key NOESY cross peak was observed between the protons at δ 2.56 and 2.18.

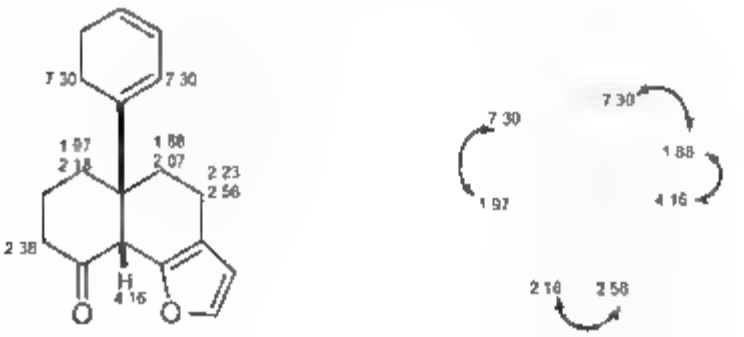


Figure 5. Selected NOESY correlations for compound **188**

The stereochemical assignment of compound **180** relies on one key long range NOESY cross peak. The long range correlation between the protons on two different methylene groups (Figure 6) could only occur in the structure as shown. All other isomers would not be expected to give this NOESY correlation.

Attempts were made to form 7- and 8-membered rings by oxidation of the furyl substituted silyl enolethers **203** and **204**, prepared by the same conjugate addition strategy (Scheme 3.4). The use of 0.1 M and 1.0 M $LiClO_4$ electrolyte solutions resulted in a poor yield of the cycloheptane **203** when **202** was oxidized. No formation of cyclic products

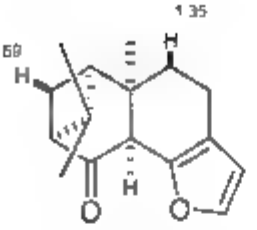
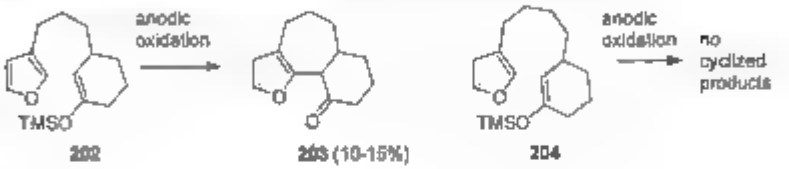


Figure 6. Key NOESY correlation observed in compound **180**



Scheme 31

from the oxidation of **204** was ever observed. These reactions had low current efficiencies relative to the consumption of the silyl enolethers. Attempts to analyze the mass balance

were frustrated by poor mass recovery. If the reaction was stopped before enolether was consumed, little could be made of the complex mixtures. There were few characteristic signals for a furan, and characteristic signals for *n*-propoxy groups were observed in the crude NMR spectra. The ketone **203** was isolated as a single isomer, but we did not determine the stereochemistry because of its impurity and the difficulty associated with obtaining adequate amounts for analysis. We cannot explain why the closure of 7- and 8-membered rings is not compatible with this strategy. Moeller[57] had demonstrated that furans would cyclize in modest to good yields with the formation of these larger rings when furan substituted alkyl enolethers were oxidized. We can only speculate that the intermediates generated from the oxidation of silyl enolethers are more reactive than

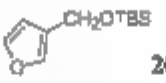
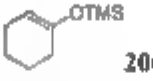
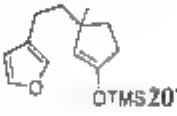
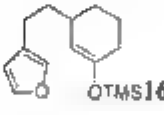
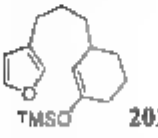
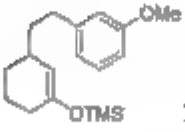
those generated from alky enolethers, hence decomposition occurs before ring c osure can occur

We stud ed the oxidation potential of the differentially substituted furans and enolethers. We hoped that enough data could be gathered to provide an explanation as to why larger rings could not be formed, and we also des red to obtain some insight into the react on mechanism. In our hands we found that cyc.ic voltammetry data was difficult to obtain precisely We suspect that our method of constructing the reference electrode .ead to slight differences between experiments, since each reference electrode was slightly different and could not be stored for extended periods of time This problem was overcome by obtaining al the data using the same reference electrode and cell construction within a short period of time We also averaged data from several experiments. and used compounds **205** and **206** as contro s.

We were always able to at least get quantat ve results from these experiments, which demonstrate the genera. trend evident from the data presented in Table 3 Al of these examples showed a single irreversible oxidation wave The simple furan **205** and the enolether **202** had the largest oxidation potentials. The simple eno.ether **206** a ways had the lowest oxidation potential by far All fury. substituted silyl enolethers that would form a 6-membered ring upon oxidation had similar potentials, such as those obtained for **207** and **162**. and these potentials were always between the oxidation potentials of **205** and **206**.

From these results we are tempted to suggest that in preparative electrolysis reactions the silyl eno.ether is oxidized first, and the furan functions as a nucleophil c terminator (see Scheme 28 path A). This conclusion is supported by Moeller's[34] work

Table 3 Cyclic voltammetery data for some furans and enolethers

entry[a]	compound	potential (V $E_{p/2}$)[b]
1	 **205**	1.3
2	 **206**	0.8
3	 **207**	1.0
4	 **162**	1.0
5	 **202**	1.3
6	 **195**	1.2

[a] Solutions were 0.01 M in analyte and 0.1 M $LiClO_4$ in acetonitrile. [b] Values were measured against a reference electrode consisting of a silver wire submerged in a 0.1 M $AgNO_3$ solution in acetonitrile and separated from the analyte solution by porous vycor

with the oxidation of furan substituted alkyl enolethers. The substrates which have higher oxidation potentials are also the substrates which gave the lowest yields in the

preparative electrolysis reactions. We cannot explain why the silyl enolether **206** has such a low oxidation potential compared with the silyl enolethers **195** and **202**.

Figure 7. Selected oxidation waves for enolethers and furans.

Conclusions

The results from the synthetic study and the analytical data presented here can be used to make some generalizations about the oxidative cyclization of organic substrates. Reactions of substrates that gave high yields would typically have low oxidation potentials and high current efficiencies. Reactions that gave poor yields had higher oxidation potentials and low current efficiencies. Other observations include the fact that reactions performed at high current density or with poor substrates would have poor mass balances, and the electrodes would typically become passivated. Furan substituted si-

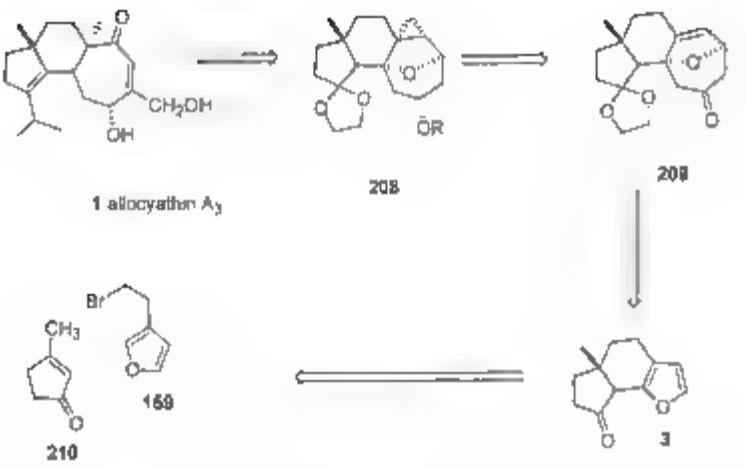
enolethers that formed 6-membered rings upon oxidation were the only substrates that formed products in synthetically useful yields.

The compatibility of this method with other functional groups has been demonstrated to some extent. The good yields and high stereoselectivity of this method make it synthetically useful in the preparation of fused polycyclic furans. A rudimentary understanding of the nature of the reaction has also been gained by exploring the oxidation of methoxybenzene substituted silyl enolethers and furan substituted enolethers that could have formed larger rings upon oxidation.

Toward the Synthesis of a Cyathane

A polycyclic furan serves as a precursor to the carbocyclic skeleton of the cyathanes in our synthetic approach to these natural products. The only other synthetic approach to the cyathanes which employs furan as a synthon is Magnus'.[37] In Magnus' approach a furan is transformed into a pyrilum ylide, which undergoes a strategic [5+2] cycloaddition reaction to form the C ring of the cyathanes.

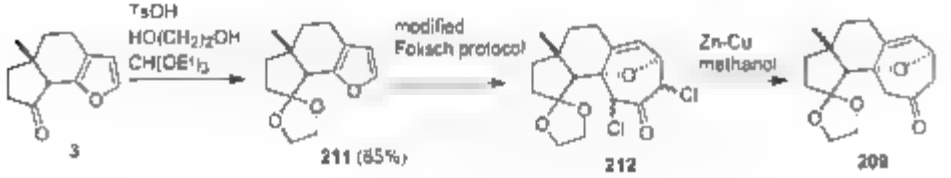
We envisioned a synthesis of a cyathane and analogues from a late stage intermediate such as **208** (Scheme 32). This intermediate contains all but one of the correct relative stereogenic centers embedded in the cyathane skeleton, and it has the functionality necessary to serve as a precursor to synthetic cyathanes. The cyclopropane could be obtained from the oxabicyclic enone **209**. This intermediate has been prepared from the polycyclic furan **3** by forming the C5-C10 and C12-C13 bonds through a strategic [4+3] cycloaddition reaction. Takeda[38] uses the same bond disconnections in his approach to the cyathanes. The furan **3** can be obtained in good yield using the new technique reported in this dissertation (*vide supra*). This method allows us to make the



Scheme 32

disconnections from the simple precursors **210** and **159**. Our strategy forms the C8-C9 bond by conjugate addition and the C3-C5 bond by anodic oxidation.

We initially chose to protect the ketone **3** as a ketal. Treatment of the ketone **3** to standard conditions for ketal formation gave **211** (Scheme 33). High yields were only obtained if the reaction mixture was purged with argon prior to addition of TsOH. We



Scheme 33

then turned our attention to the cycloaddition reaction of **211**. There has been only one report of a [4+3] cycloaddition reaction with a fused furan. This was in Chang's[78] colchicine synthesis. Of all the protocols reported for the [4+3] oxyallyl cycloaddition only the method described by Folsch[79,80] gave the desired product, although in low yield. Modified conditions gave a high conversion of **211** to a mixture of epimers **212**. These

conditions generated the oxyallyl species slowly. This was accomplished by a simultaneous and portion-wise addition of two separate solutions, one of $NaOCH_2CF_3$ and the other of 1,1,3-trichloroacetone, to neat **211**. We did not determine the stereochemistry of the dichlorides **212**, but equilibration takes place during the reaction to give only two compounds.

Instead of determining the stereochemistry of **212** we decided that dechlorination would allow us to determine if the cycloaddition reaction had been selective. Dechlorination of **212** with Zn-Cu couple gave only the ketone **209**, but we found that both the starting materials and the product were sensitive to the reaction conditions. Heating of the reaction mixture or allowing the mixture to become acidic led to decomposition. We found that using a large excess of Zn-Cu couple and sonication led cleanly to **209**. The stereochemistry of **209** was assigned initially by NMR correlation experiments and later confirmed by X-ray crystallography. We now had access to a compound with the carbocyclic system of the cyathanes in good overall yield and excellent stereoselectivity.

The selectivity of the cycloaddition reaction is attributed to the *cis* 5-6 ring fusion present in the starting material. The oxyallyl species must approach the furan *syn* to the methyl group at C9. The 3-dimensional structure of ketal **211** is likely responsible for the observed stereoselectivity. The *cis* fused ring system has a shape with a convex and concave face. The convex face of the molecule must be more accessible to the oxyallyl species despite the presence of the C9 methyl group.

We now hoped to use the 3-dimensional structure of the new oxabicyclic system in ketone **209** to control subsequent transformations. Specifically, we desired to add the

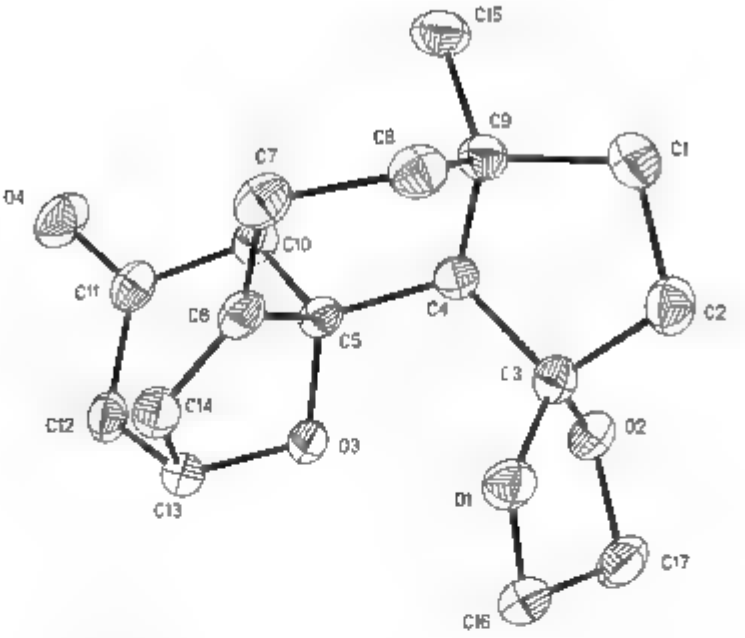
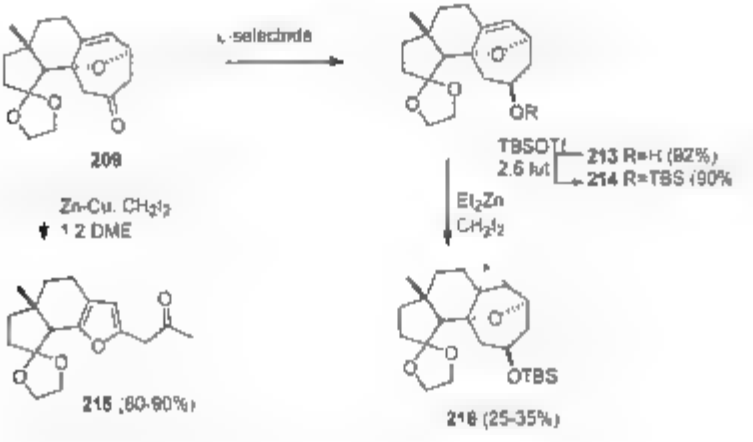


Figure 8 X-Ray crystal structure of **198**.

C16 carbon of the natural products by reaction of the double bond. Initial efforts focused on the use of cyclopropanating reagents. The first attempt was made using classical Simmons-Smith conditions. No reaction was observed when **209** was treated with Zn-Cu couple and CH_2I_2 in boiling diethyl ether. Heating in 1,2-dimethoxyethane as solvent under the same conditions, led to the rearrangement product **215** as the exclusive product (Scheme 34). We suspected that residual acid present from the preparation of the Zn-Cu couple was responsible for the observed reaction, but control experiments revealed that only the mixture of Zn-Cu couple and CH_2I_2 caused the fragmentation to occur. If the zinc carbenoid is not responsible, then zinc salts formed due to the presence of adventitious atmosphere are likely the cause. Fragmentation reactions of oxabicyclic

ketones such as **209** have been reported,[8] though these reactions employed strong acids. Attempts to use the Furukawa protocol[82] (Et_2Zn-CH_2I_2) to form a cyclopropane led to decomposition of the substrate



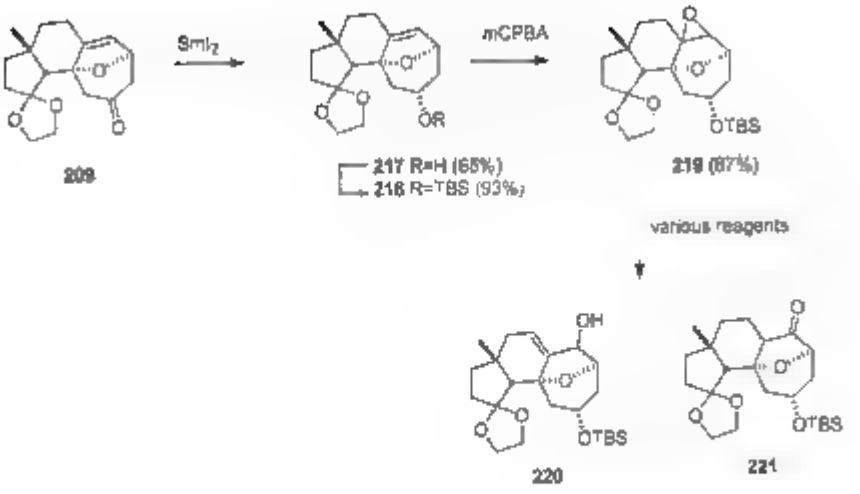
Scheme 34

The instability of **209** was due in part to the carbonyl and its position in the oxabicyclic system.[81] We therefore sought to remove this decomposition pathway by reduction of the ketone. We initially tried reduction of the ketone **209** using DIBAL and discovered that the reduction was selective in about a 4:1 ratio. Reduction with L-selectride provided the alcohol **213** selectively and in good yield. We did not determine the stereochemistry at this stage because there is ample precedent to predict the stereochemical outcome of ketone reductions in these bicyclic systems.[83] Protection of the alcohol as a TBS ether provided **214**. Reaction of the olefin **214** with Et_2Zn-CH_2I_2 provided a low yield of the cyclopropane **216**. The stereochemistry of the cyclopropane **216** was determined by NMR correlation experiments. A key cross peak in the NOESY spectrum between the α hydrogen on the cyclopropane and a hydrogen on one of the acetal carbons was observed. Modeling of the two different possible cyclopropanes

reveals that only such a cross peak would be observed in **216**. Observation of this cross peak in the diastereomer would be unlikely

Figure 9 Key NOESY cross peaks observed in **216**.

Some attempts to optimize the cyclopropanation reaction were made, but these were not successful. Apparently the acetal **214** was unstable to the reaction conditions. We attempted to move the double bond out of the oxabicyclic system and change the oxidation state of C14 to the same as that found in the natural product. Reduction of ketone **209** was carried out using SmI_2[83] (Scheme 35), since this reducing agent had been reported to give the opposite selectivity of L-selectride. Reduction with SmI_2 was predicted to give the same stereochemistry at C11 as that found in the natural products. Proof of this was obtained by comparing the spectroscopic properties of the alcohol **217** with those of alcohol **213**. Protection of the alcohol under standard conditions gave the silyl ether **218**. The epoxide **219** was then formed by the action of *m*CPBA. The olefin **218** was extremely reactive to these conditions.

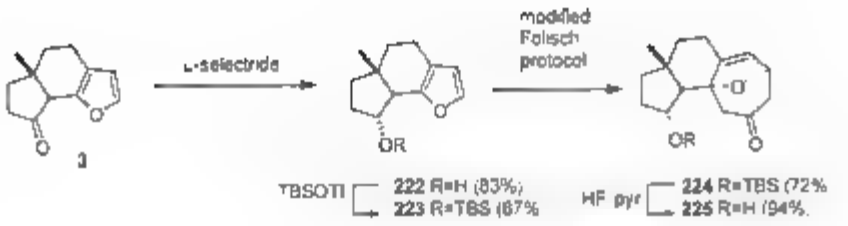


209 217 R=H (65%) 216 R=TBS (93%) 218 (87%) 220 221

Scheme 35

There are many methods reported to obtain either a ketone or allylic alcohol by isomerization of an epoxide. Attempts to isomerize the epoxide were frustrated by decomposition, attributed to the reactivity of the ketal. Two different isomeric products were also formed in most cases. These products were tentatively assigned the structures **220** and **221**. Because of these difficulties we abandoned this route in the early stages of investigation. We did observe that heating the epoxide in toluene in the presence of basic alumina resulted in the formation of **220** exclusively, but no optimization of this reaction was attempted. We attempted cyclopropanation of **220**, but found it to be unreactive. This could be due to a misassigned structure or to problems associated with carrying out the reaction on a small scale.

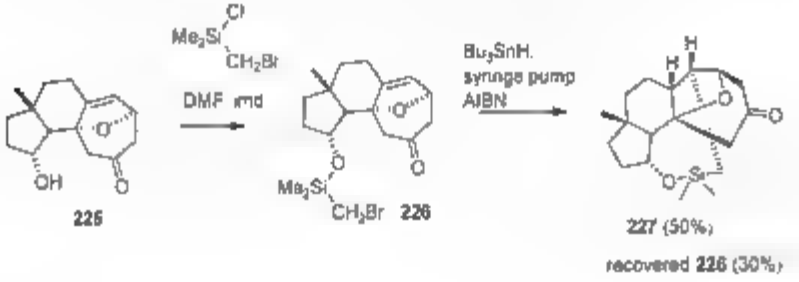
We choose to modify our strategy by changing the oxidation state at C3 prior to formation of the oxabicyclic system. We hoped that an alcohol at this position would serve as a handle to deliver the required carbon in a controlled manner. Reduction of **3** with L-selectride gave the alcohol **222** selectively (Scheme 36). Care had to be taken in



Scheme 36

the reduction because of the ease of enolization of the ketone **3**. Only the slow addition of a solution of the ketone **3** to a cold L-selectride solution resulted in clean reduction. Attempts to reduce the ketone with $NaBH_4$ under conditions where enolization was reversible were not selective. Protection of the alcohol as the silyl ether gave **223**. Using the same cycloaddition reaction conditions as those employed in the synthesis of **209**, furan **223** was converted to the oxabicyclic ketone **224**. Again, the *cis* 5-6 ring fusion appears to control the selectivity of the reduction and cycloaddition reactions.

Our first attempts to introduce the angular methyl group into this substrate relied upon a radical cyclization strategy. Alcohol **225** was converted the bromomethyl silane **226** (Scheme 37). We carried out the reaction in dilute solution with a syringe pump



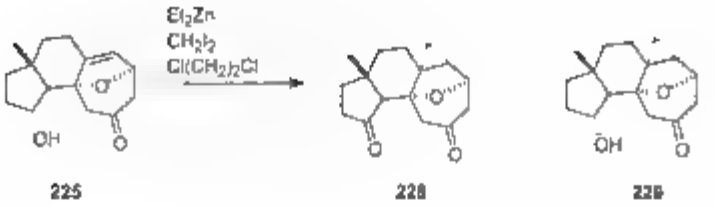
Scheme 37

addition of Bu_3SnH. Only one product, the ketone **227**, formed in the reaction. We also recovered starting material and attributed this to the difficulty of removing adventitious

oxygen from a reaction of this scale (about 0.04 mmol). To our surprise, cyclization had occurred in an 8-*endo* fashion. The steric hinderance of a 7-*exo* closure must be the controlling factor. The termination of the radical by hydrogen abstraction is selective because the cage like structure that is formed makes abstraction from the other face unfavorable. The regio and stereochemistry were determined by NMR correlation experiments. The regiochemistry was easily proven by the coupling system that was observed in which the methylene hydrogens α to silicon were not isolated. If the 7-*endo* closure had occurred, then these diastereotopic hydrogens would only have strong couplings with each other.

We next explored the cyclopropanation of substrate **225**. Even though the oxabicylic system had proved too reactive in the case of **209**, the greater directing effect of the alcohol in **225** could make the reaction faster, possibly removing the olefin and the decomposition pathway more quickly than fragmentation could occur.

We studied the reaction conditions, relying on the work of Denmark[84,85] that demonstrated that 1,2-dichloroethane was the best solvent for the reaction and that $ClCH_2I$ formed a more reactive carbenoid when reacted with Et_2Zn. Reactions employing $ClCH_2I$ as a carbenoid precursor resulted in the rapid decomposition of our substrate. This was attributed to the greater Lewis acidity of the zinc halide salt that is formed, which then reacts with the oxabicyclic system to cause decomposition. When the reaction was performed using CH_2I_2 as the carbenoid precursor and dichloroethane as solvent we were surprised to find that the diketone **228** was obtained as the major product in a short reaction time (Scheme 38). A minor amount of the cyclopropane-alcohol **229** was also formed, but this compound proved to be inseparable from the starting material



225 228 229

Scheme 38

We made the stereochemcial assignments of **228** based on NMR correlation experiments. The rigid nature of the structure and good resolution of the spectra allowed unambiguous assignments to be made. A key cross peak in the NOESY spectrum between the cyclpropane proton and an α-carbonyl proton was our key assignment.

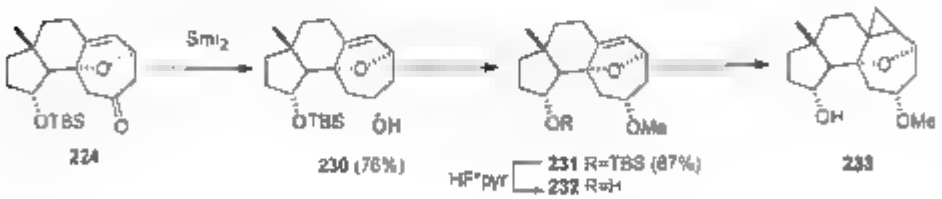
Figure 10. Key NOESY correlation observed in compound **228**.

We suspected that oxygen present in the mixture was responsible for the oxidation of **225**. We repeated the experiment on several occasions with rigorously degassed solvent. We did not observe any appreciable oxidation in these cases, yet we were frustrated because the reaction would not reach completion. If the reaction was heated or kept for prolonged reaction times, then decomposition would occur. We were unable to

obtain a sample of **229** in a form pure enough for determination of the stereochemistry. The stereochemistry of **229** is assigned based on the structure determined for **228** under the assumption that **229** is a precursor to **228**.

There is some indication that oxygen may increase the rate of cyclopropanation of olefins in the Et_2Zn-CH_2I_2 system.[86,87] If this is true, then the sluggish reaction of **225** under rigorously deoxygenated conditions can be explained. The rapid reaction of **225** to form the diketone **228** in solvent that contains oxygen is due to the accelerating effects of oxygen, and the oxygen must also be responsible for the oxidation of the alcohol. Under degassed conditions the reaction proceeds more slowly, allowing decomposition by fragmentation of the oxabicyclic system to occur at a rate competitive with cyclopropanation.

We now sought to test this hypothesis by reduction of the ketone, thereby removing the proposed decomposition pathway of the substrate. Reduction of the ketone **224** with SmI_2 provided the alcohol **230** in good yield (Scheme 39). We assigned the



Scheme 39

stereochemistry by preparation of the diasteromeric alcohol *via* reduction with L-selectride. The precedent for reduction selectivity with the two different reagents and the fact that different alcohols are formed in each reaction allows us to assign the structures as shown. We then chose to make the methyl ether of the alcohol **230**. Though the

choice of a methyl ether as a protecting group is generally a poor one, we only wished to test our hypothesis. We would be concerned about protecting group strategy at a latter point if cyclopropanation of the olefin was successful. After formation of the methyl ether **231** the TBS ether was cleaved with HF•pyridine to provide the alcohol **232**. Reaction of this substrate with Et_2Zn-CH_2I_2 with the removal of oxygen led cleanly to the cyclopropane **233**. We were only able to obtain qualitative results on a small scale and have therefore not reported a percent yield. Qualitatively, the reaction seems to proceed without decomposition and little oxidation of the alcohol is observed. This reaction has not been optimized and coworkers are currently seeking more information about this reaction.

Conclusions

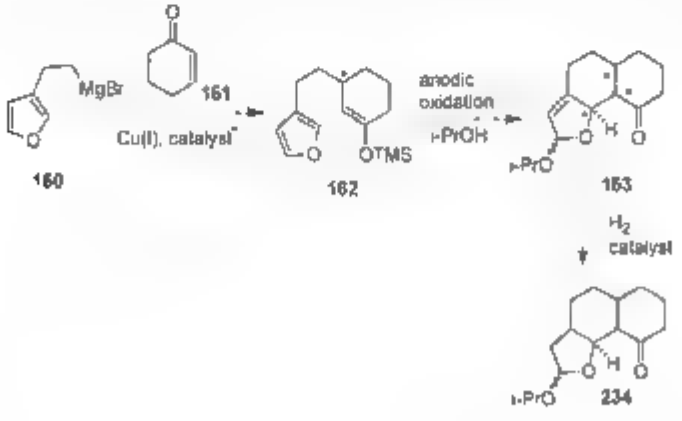
A new synthetic approach to the cyathanes has been explored, which proves the usefulness of the method of forming polycyclic furans reported in the first section of Chapter 3. The use of a [4+3] cycloaddition reaction as a key step has also been demonstrated, and generalizations about this reaction can be made. The reactivity of the fused oxabicyclic system has also been investigated, and a better understanding of the reactivity of these systems has been gained. Useful methods for introducing the needed carbon atoms and functionality in an approach to the cyathanes have been discovered.

Though a cyathane has yet to be synthesized with this route, further work can demonstrate whether or not this goal can be accomplished. The synthesis of compounds such as **216** and **233** give support to the idea that this route will eventually yield a synthetic cyathane.

CHAPTER 4
CONCLUSIONS AND FUTURE WORK

The initial investigations into the synthetic method reported in this dissertation indicate that useful compounds and compounds of unique structure can be synthesized. Further work to understand the full synthetic utility and mechanistic details of this anodic oxidation reaction is required. A total synthesis of the cyathanes has not been achieved nor have the synthesis of analogous structures, yet the results indicate that relatively few steps are required to reach this goal.

In our method, two contiguous stereocenters are set by the conjugate addition-anodic oxidation reactions, yet one other stereocenter is set in the initial oxidation reaction that is lost on workup. The synthetic utility of the intermediate **163** has not been explored. As an example, if hydrogenation of the unstable intermediate **163** to form **234** (Scheme 40) could be done, then reversion to the furan cannot occur. A variety of

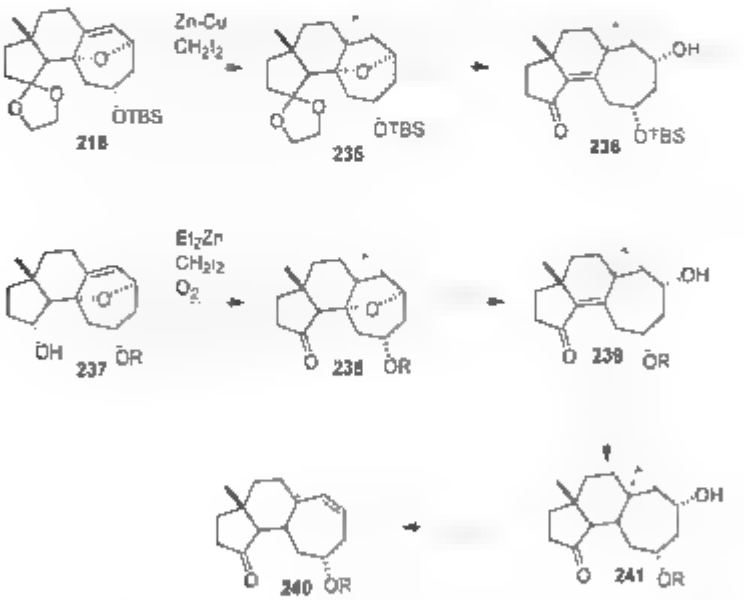


Scheme 40

interesting compounds could be envisioned to arise from a precursor such as **234**.

This strategy could also be implemented asymmetrically, because there are a number of reports of asymmetric conjugate addition reactions.[88,89] If the conjugate addition can be carried out in high enantiomeric excess, then non-racemic compounds with four contiguous stereocenters could be made in only three steps from materials without any stereogenic centers.

Research is still needed to understand the complex oxabicyclic system present in compounds such as **218**. Some possibilities that have not been explored include an attempt to cyclopropanate **218** under less reactive conditions (Scheme 41). We



Scheme 41

believe that the Furukawa protocol causes decomposition of **218** because of the ketal functionality. If **235** could be formed, then hydrolysis of the ketal and elimination of the oxo-bridge would form the compound **236**. In the same general way, we could take

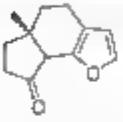
advantage of the oxidation of the alcohol **237** using the Furukawa protocol. A ketone such as **238** could be formed in one step. Elimination of the oxo-bridge would provide **239**. The next step is to see if the stereogenic center at C5 can be introduced by reduction of the olefin to form **241**. Deoxygenation of 241 by a method that proceeds through a radical intermediate[90] would open the cyclopropane and form an olefin that could be used to introduce the functionality needed to complete a total synthesis.

CHAPTER 5
EXPERIMENTAL

General No special precautions were made to exclude atmosphere from electrolysis reactions. All other non-hydrolytic reactions were performed under an atmosphere of argon and in glassware dried with a flame. Preparative electrolysis was done with an Amel Instruments general purpose potentiostat model 2049. Cyclic voltammetry experiments were performed with an EG&G Princeton Applied Research potentiostat model 263A at a scan rate of 20 mV/s in solutions 0.1 M in $LiClO_4$ and 0.0 M in analyte. Oxidation potentials were measured against a reference electrode consisting of a silver wire submerged in a 0.1 M $AgNO_3$ solution in acetonitrile and separated from the analyte solution by porous vycor. All electrode materials were obtained from Electrosynthesis Inc. THF, diethyl ether and 1,2-dimethoxyethane (DME) were distilled from sodium and/or potassium benzophenone. Dichloromethane and 1,2-dichloroethane were distilled from CaH_2. All other materials were obtained from commercial sources. These materials were purified by standard procedures if necessary. When mixtures of TMSCl-Et_3N (1:1) are used, this refers to the supernatant fluid removed from a centrifuged mixture. Thin layer chromatography was done on EM Science glass backed F_{254} silica gel plates and visualized with UV light, iodine and by charring with EtOH-H_2SO_4 mixtures. Preparative chromatography was performed in the manner of Still[9] with N_2 pressure on Natl and International Corp 200-300 mesh silica gel.

NMR spectra were recorded at 300 MHz (^{1}H) in $CDCl_3$ using Varian (Mercury Gemini, VXR) instruments unless otherwise stated. NMR spectra obtained at 500 MHz

(^{1}H) were recorded on a Varian INOVA. Mass spectra were provided by the University of Mass Spectrometry service. Combustion analysis was performed by Atlantic Microlabs. IR spectra were recorded on a Perkin-Elmer FT-IR. Melting points were obtained on a Thomas Hoover Mel-temp and are uncorrected. All NMR correlations were provided by or with the assistance of Dr. Ion Ghiviriga of the University of Florida NMR facilities.



5a-Methyl-4,5,5a,6,7,8a-hexahydro-1-oxa-as-indacen-8-one (3). A solution of 2-(3-furyl)-ethylbromide[68] (1.67g, 9.5 mmol) in THF (9.5 mL) purged with argon while stirring the solution for 10 min. This solution was then added to a flask containing Mg turnings (0.23 g, 9.5 mmol). After 2.5 h the majority of the Mg had dissolved and a clear dark solution had formed. The solution was cooled to 0°C and CuI (0.36 g, 1.9mmol) was added. After stirring for 5 min the turbid black solution was cooled to -78°C. A mixture of TMSCl-Et$_3$N (9.5 mL) was added, followed by the addition of 3-methyl-2-cyclopentenone (0.785 mL, 8.0 mmol). The mixture turned bright yellow upon addition of the enone. The mixture was allowed to warm to rt over 5 h and then placed in the refrigerator overnight. The black mixture was then poured into an ice-cold mixture of hexanes (100 mL) and saturated aqueous NH_4Cl (50 mL). The hexanes layer was separated and washed with $NaHCO_3$, then brine, and dried over Na_2SO_4. Removal of solvent provided the crude enolether (2.0 g, ^{1}H NMR δ 7.34 (m, 1H), 7.20 (m, 1H), 6.26 (m, 1H), 4.53 (t, J = 1.8 Hz, 1H), 2.35 (m, 4H), 1.76 (m, 1H), 1.58 (m, 3H), 1.05 (s, 3H), 0.02 (s, 9H), ^{13}C NMR δ 153.2, 142.6, 138.4, 125.8, 111.8, 111.0, 45.0, 43.0, 34.8, 33.2,

28.0, 20.6, 0.0. A 1000-mL beaker was charged with the crude enolether, 2,6-lutidine (3.5 mL, 30 mmol), 2-propanol (74 mL), MeCN (290 mL), and $LiClO_4$ (11.8g), and the mixture was stirred until homogeneous. An electrode system (Figure 1.1) consisting of alternating plates of carbon (anode) and steel (cathode) was inserted and charged with a constant current of 16.6 mA. There was ca. 65 cm^2 of carbon charged as the anode. The reaction mixture was partially covered with PTFE tape to slow evaporation of solvent, and after 25.5 h the current was turned off. The volatiles were removed under vacuum, and the crude material was dissolved in ether (150 mL) and washed with 1 M HCl. The aqueous phase was extracted with Et_2O (2*25 mL), and the combined organic phases were washed with water, $NaHCO_3$, brine and dried over $MgSO_4$. After filtration and evaporation of solvent the crude product was purified by chromatography (9:1 hexanes: ethyl acetate) to provide the ketone **3** as a pale yellow oil (2.19 g, 78%). Freezing of this sample in liquid N_2 under vacuum followed by trituration with cold pentane provided an analytical sample as a white solid: mp 42-43°C; R_f (9:1 hexanes: EtOAc) = 0.27; IR (KBr pellet) ν_{max} 2959, 2862, 1742, 1625, 1550, 1050, cm^{-1}; ^1H NMR δ 7.35 (dd, J = 1.9, Hz, 1H), 6.21 (J = 1.9 Hz, 1H), 3.00 (s, 1H), 2.51 (m, 2H), 2.41 (m, 2H), 2.00 (m, 1H), 1.81 (m, 1H), 1.62 (m, 2H), 1.19 (s, 3H); ^{13}C NMR δ 215.1, 144.7, 142.6, 116.7, 110.0, 54.9, 40.2, 35.5, 33.1, 31.7, 25.5, 19.0; EI-HRMS *m/z* calculated for $C_{12}H_{14}O_2$ (M$^+$) 190.0994, found: 190.0993; Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42; found: C, 75.64; H, 7.5.

2-(3-Furyl)-ethanol (148). A solution of 3-bromofuran **158** (5.4mL, 60.6 mmol) in THF (100 mL) was cooled to -78°C, and a solution of *n*-BuLi (2.6 M, 23.3 mL, 60.6 mmol) was added slowly *via* an addition funnel over 30 min. The resulting solution was

stirred for 1 h. A solution of ethylene oxide (3.2 g, 72 mmol) in THF (20 mL) was added over 5 min, and then BF_3•OEt_2 (9.2 mL, 72.7 mmol) was added via addition funnel over 30 min. The resulting solution was stirred for 5 h. Saturated $NaHCO_3$ was added slowly over 15 min, and the semi-solid mixture was allowed to warm slowly to rt over 3 h. The aqueous phase was extracted with EtOAc (2*30 mL), and the combined organic phases were washed with saturated $NaHCO_3$ and brine. The solution was dried with $MgSO_4$ and after evaporation of solvent the crude product distilled (64-68° C, 2.5 mmHg) to provide the alcohol **148** as a clear liquid (3.7 g, 54%) having physical and spectroscopic properties consistent with those reported.[68]

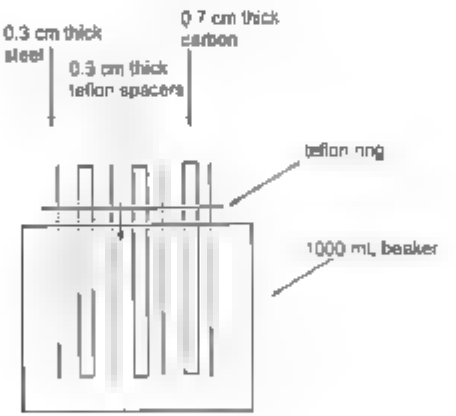
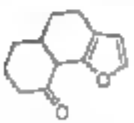
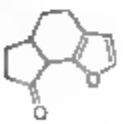


Figure 11. Schematic of electrode system used in synthesis of **3**



***cis*- 4,5a,6,7,8,9a-Hexahydro-5H-naphtho[1,2-b]furan-9-one (164).** A solution of Grignard reagent **160** (0.54 M, 0.890 mL, 0.48 mmol) was stirred and cooled to 0°C. Copper(I) iodide (10 mg, 0.05 mmol) was then added. The mixture was stirred for 5 min and cooled to -78°C. Neat TMEDA (0.072 mL, 0.48 mmol) was added over 2 min. A

mixture of TMSCl:Et$_3$N (0.70 mL) was added over 2 min. followed by the addition of 2-cyclohexen-1-one (0.039 mL, 0.40 mmol). The reaction mixture was allowed to slowly warm to rt over 8 h. The work up procedure was carried out as described for **3**. The crude silyl enolether was isolated as a pale yellow oil (95 mg). The silyl eno ether was dissolved in electrolyte solution (13.0mL, 0.1 M $LiClO_4$, 0.04 M 2,6 lutidine) and then added to a 3-neck 25-mL flask. In each of the necks of the flask was inserted a carbon rod (0.5 cm in diameter) "pushed through" a rubber septum. The central rod was connected to the potentiostat as the anode while the flanking rods were both used as counter electrodes (Figure 12). A constant current of 0.362 mA was passed for 20 h (ca. 2.0 F/mol). Workup was performed in the same manner as described for **3**. After chromatography (9:1 Hex:EtOAc) the ketone **164** was isolated as a pale yellow oil (52 mg, 68%): R_f (9:1 hexanes:EtOAc) = 0.26; IR (neat) υ_{max} 2930, 1715, 1631, 1503, 1253, 1107 cm^{-1}; ^{1}H NMR δ 7.32 (d, J = 1.9 Hz, 1H), 6.23 (d, J = 1.9 Hz, 1H), 3.63 (d, J = 5.7 Hz, 1H), 2.61-2.43 (m, 3H), 2.42-2.28 (m, 2H), 2.00-1.84 (m, 3H), 1.84-1.72 (m, 1H), 1.72-1.60 (m, 2H); ^{13}C NMR δ 209.8, 147.0, 142.2, 117.7, 110.4, 50.6, 40.7, 38.8, 28.6, 26.7, 24.1, 20.5; EI-HRMS *m/z* calculated for $C_{12}H_{14}O_2$ (M$^+$) 190.0994, found 190.1029.



***cis*-4,5,5a,6,7,8a-Hexahydro-1-oxa-as-indacen-8-one (176).** Using the same general procedure as described for **164**, 2-cyclopenten-1-one (0.065 mL, 0.78 mmol) was reacted to give **176** as a pale yellow oil (88 mg, 64%) after chromatography: R_f (10:1 hexanes:EtOAc) = 0.30; IR (neat) υ_{max} 2855, 1743, 1627, 1454, 1122, 1094 cm^{-1}; ^{1}H

NMR δ 7.36 (dd, J = 0.6, 2.0 Hz, 1H), 6.21 (d, J = 2.0 Hz, 1H), 3.38 (d, J = 7.3 Hz, 1H), 2.75 (m, 1H), 2.51 (m, 2H), 2.36 (m, 2H), 2.12 (m, 1H), 1.90 (m, 2H), 1.68 (m, 1H). ^{13}C NMR δ 215.2, 144.7, 142.6, 118.1, 110.3, 48.3, 36.7, 36.3, 25.7, 25.5, 20.2; EI-HRMS m/z calculated for $C_{11}H_{12}O_2$ (M$^+$): 176.0837, found: 176.0839

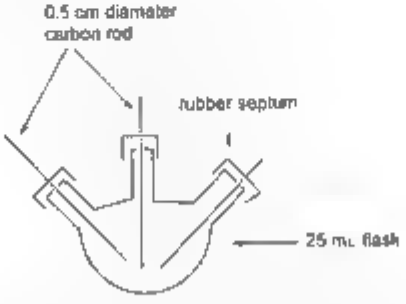
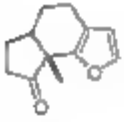
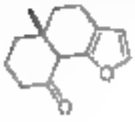


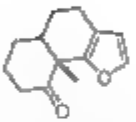
Figure 12. Schematic of electrode system used in synthesis of **164**



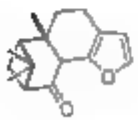
***cis*-8a-Methyl-4,5,5a,6,7,8a-hexahydro-1-oxa-as-indacen-8-one (177).** Using the same general procedure as for **164**, 2-methylcyclopentenone (0.023 mL, 0.24 mmol) was reacted to give the ketone **177** as a colorless oil (29mg, 64%), after chromatography: R_f (9:1 hexanes:EtOAc) = 0.27; IR (neat) υ_{max} 2927, 2854, 1745, 1629, 1227, 1054 cm^{-1}; ^1H NMR δ 7.33 (d, J = 1.8 Hz, 1H), 6.17 (d, J = 1.8 Hz, 1H), 2.55-2.45 (m, 2H), 2.40-2.22 (m, 3H), 2.00-1.75 (m, 2H), 1.38 (s, 3H); ^{13}C NMR δ 18.9, 21.3, 22.4, 23.2, 36.2, 44.3, 49.9, 110.2, 117.5, 142.5, 147.8, 217.8; EI-HRMS m/z calculated for $C_{13}H_{14}O_2$ (M$^+$): 190.0994, found: 190.0989



***cis*-5a-Methyl-4,5a,6,7,8,9a-hexahydro-5H-naphtho[1,2-b]furan-9-one (178).** Using the same general procedure as for **3**, 3-methyl-2-cyclohexen-1-one (0.77 mL, 7.2 mmol) was reacted to give the ketone **178** as a pale yellow oil (1.12g, 76%) after chromatography. R_f (9:1 hexanes:EtOAc) = 0.27, IR (neat) υ_{max} 2924, 1716, 1632, 1455, 1230 cm^{-1}, ^{1}H NMR δ 7.31 (d, J = 1.8 Hz, 1H), 6.23 (d, J = 1.8 Hz, 1H), 3.23 (s, 1H), 2.52 (m, 2H), 2.30 (m, 2H), 1.88 (m, 3H), 1.71 (m, 1H), 1.48 (m, 2H), 1.09 (s, 3H); ^{13}C NMR δ 21.03, 147.3, 142.4, 116.5, 110.4, 56.9, 39.8, 39.7, 34.3, 33.4, 26.7, 22.3, 19.0; EI-HRMS *m/z* calculated for $C_{13}H_{16}O_2$ (M^+): 204.1150, found: 204.1172.

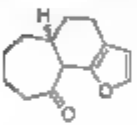


***cis*-9a-Methyl-4,5a,6,7,8,9a-hexahydro-5H-naphtho[1,2-b]furan-9-one (179).** Using the same general procedure as described for **164**, 2-methyl-2-cyclohexen-1-one (20 mg, 0.18 mmol) was reacted to give **179** as a colorless oil (24mg, 65%) after chromatography. R_f (9:1 hexanes:EtOAc) = 0.28, IR (neat) υ_{max} 2927, 2851, 1707, 1628 1163 cm^{-1}, ^{1}H NMR δ 7.31 (d, J = 1.9Hz, 1H), 6.24 (d, J = 1.9Hz, 1H), 2.62-2.40 (m, 4H), 2.22 (m, 1H), 2.09 (m, 1H), 2.20-1.66 (m, 5H), 1.47 (s, 3H); ^{13}C NMR δ 20.0, 22.4, 24.7, 25.8, 26.8, 39.2, 45.2, 51.3, 110.5, 116.3, 142.1, 151.3, 211.9; EI-HRMS *m/z* calculated for $C_{13}H_{16}O_2$ (M^+): 204.1150, found: 204.1166.



Ketone 180. Using the same procedure as described for **164**, verbenone (50% ee, 0.031 mL, 0.20 mmol) was reacted to provide the ketone **180** as a yellow solid (72mg,

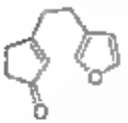
69%) after chromatography: R_f (1:1 hexane:EtOAc)= 0.29; mp 121°C (decomp); IR (KBr) υ_{max} 2906, 1711, 1633, 1479, 1029 cm^{-1}; ^{1}H NMR δ 7.42 (dd, J= 10.2, 1.9 Hz, 1H), 6.23 (d, J = 1.9 Hz, 1H), 3.45 (s, 1H), 2.70 (3 line m, 1H), 2.58 (5 line m, 1H), 2.50 (m, 1H), 2.48 (dd, J = 12.7, 3.8 Hz, 1H), 2.04 (3 line m, 1H), 1.87 (m, 1H), 1.69 (d, J = 11.3 Hz, 1H), 1.43 (s, 3H), 1.35 (dt, J = 4.3, 3.3 Hz, 1H), 1.24 (d, J = 7.0 Hz, 3H), 1.23 (s, 3H); ^{13}C NMR δ 209.0, 146.4, 142.7, 118.5, 110.1, 58.8, 54.2, 50.6, 40.3, 37.8, 34.8, 28.1, 26.8, 25.8, 25.7, 18.7; EI-HRMS *m/z* calculated for $C_{16}H_{20}O_2$ (M$^+$): 244.1463, found 244.1463



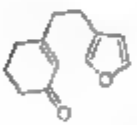
4,5,5a,6,7,8,9,10a-Octahydro-1-oxa-cyclohepta[e]inden-10-one (181). Using the same general procedure as described for 3, 2-cyclohepten-1-one (0.405 mL, 3.64mmol.) was reacted to give **170** as a mixture of two isomers in a 4:1 ratio isolated as a colorless oil (430mg, 58%) after chromatography. The two isomers could not be separated. Continued chromatography allowed full characterization of the major product.

major *trans* **181**: R_f (9:1 hexanes:EtOAc) = 0.25; IR (neat) υ_{max} 2925, 1711, 1637, 1504, 1158 cm^{-1}; ^{1}H NMR δ 7.29 (dd, J = 0.9, 1.7 Hz, 1H), 6.21 (d, J = 1.7 Hz, 1H), 3.92 (d, J = 9.7 Hz), 2.76 (m, 1H), 2.50 (m, 2H), 2.08-1.94 (m, 2H), 1.94-1.76 (m, 2H), 1.76-1.55 (m, 2H), 1.38-1.55 (m, 2H), 1.38-1.20 (m, 2H); ^{13}C NMR δ 212.2, 148.1, 141.9, 120.3, 110.2, 52.1, 44.7, 40.8, 38.7, 32.3, 27.7, 23.2, 21.9; EI-HRMS *m/z* calculated for $C_{13}H_{16}O_2$ (M$^+$): 204.2649, found:204.1189

minor *cis* **181** (partial): H NMR δ 7.27 (d, *J* = 1.7 Hz, 1H), 6.23 (d, *J* = 1.7 Hz, 1H), 4.10 (d, *J* = 7.2 Hz, 1H), ^{13}C NMR δ 211.1, 147.7, 142.0, 119.9, 110.4, 49.8, 42.7, 36.1, 32.9, 28.2, 24.8, 24.4, 21.3.

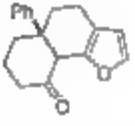


3-(2-Furan-3-yl-ethyl)-cyclopent-2-enone (185). Using the same general procedure as described for **186** (*vide infra*). 2-cyclopenten-1-one (0.50 mL, 6.0 mmol) was reacted to form **185**, isolated as colorless oil (420 mg, 40%) after chromatography: R_f (1:1 Hex: EtOAc) = 0.29, IR (neat) υ_{max} 3131, 2922, 1706, 1615, 1501, 1437, 1185, 1025, H NMR δ 7.37 (m, 1H), 7.25 (m, 1H), 6.28 (m, 1H), 6.00 (m, 1H), 2.79-2.64 (m, 4H), 2.60 (m, 2H), 2.41 (m, 2H); ^{13}C NMR δ 209.8, 181.5, 143.0, 138.9, 129.8, 123.5, 110.5, 35.2, 33.7, 31.5, 22.4, EI-HRMS *m/z* calculated for $C_{11}H_{12}O_2$ (M^+): 176.0837, found: 176.0836.



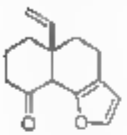
3-(2-Furan-3-yl-ethyl)-cyclohex-2-enone (186). The Grignard reagent **126** was generated as described in the synthesis of **3** from **159** (1.0g, 5.7 mmol) and the mixture was diluted with THF (10mL) after complete formation of the Grignard reagent. 2-Cyclohexen-1-one (0.500 mL, 5.2 mmol) was then added dropwise over 10 min. After 1 h, the mixture was cooled to 0°C and saturated aqueous NH_4Cl (10mL) was added. The layers were separated and the aqueous layer was extracted with EtOAc (3*5mL). The combined extracts were washed with brine, dried with $MgSO_4$, filtered and the solvent evaporated to provide the crude alcohol (865mg). This material was dissolved in CH_2Cl_2

(8 mL) and NaOAc (110mg, 1.36mmol) was added. The mixture was cooled to 0° C and PCC (1.45g, 6.73mmol) was added at once. The mixture was allowed to warm to rt. After 1h at rt silica gel was added (ca. 2g) and a spatula tip of charcoal. The mixture was diluted with Et_2O (15 mL) and filtered through a plug of celite. The plug was washed with several small portions of ether. After evaporation of solvent, purification by flash chromatography (1:1 Hex:EtOAc) provided **186** (430mg, 44%) as a colorless oil. R_f (1:1 hexanes:EtOAc) = 0.26. IR υ_{max}: 2931, 1666, 1626, 1252, 1021 cm^{-1}. ^{1}H NMR δ 7.35 (m, 1H), 7.23 (m, 1H), 6.27 (m, 1H), 5.89 (m, 1H), 2.65 (t, J = 7.1Hz, 2H), 2.47 (t, J = 7.6 Hz, 2H), 2.38-2.28 (m, 4H), 2.03-1.94 (m, 2H). ^{13}C NMR δ 199.8, 165.3, 143.0, 139.0, 126.1, 123.7, 110.8, 38.2, 37.4, 29.8, 22.7, 22.4. EI-HRMS *m/z* calculated for $C_{12}H_{14}O_2$ (M^+): 190.0994, found 190.0996.

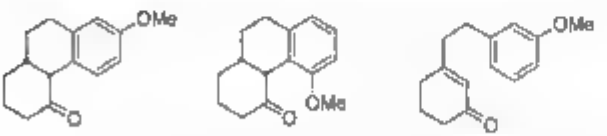


***cis*-5a-Phenyl-4,5a,6,7,8,9a-hexahydro-5H-naphtho[1,2-b]furan-9-one (188).** Enone **186** (78mg, 0.41 mmol) was reacted with excess phenyl cuprate generated from CuI, and phenyl magnesium bromide (0.80 mmol) in THF (1.5 mL), TMSCl/Et_3N (1.0 mL) and TMEDA (0.075 mL, 1.0 mmol). The crude material was isolated and was subjected to the same electrolysis conditions as those described for **164** to provide **188** after chromatography as a colorless oil, which solidified in the refrigerator (78mg, 71%). R_f (10:1 hexanes:EtOAc) = 0.23. IR υ_{max} (neat): 2917, 2849, 1714, 1637, 1499, 1462, 1034 cm^{-1}. ^{1}H NMR δ 7.43 (dd, J = 0.7, 1.9 Hz, 1H), 7.34-7.29 (m, 4H), 7.25-7.21 (m,1H), 6.17 (d, J = 1.9 Hz, 1H), 4.16 (s, 1H), 2.60-2.50 (m, 1H), 2.36 (t, J = 7.4 Hz, 2H), 2.26-2.12 (m, 2H), 2.11-2.04 (m, 2H), 2.00-1.94 (m, 1H), 1.91-1.82 (m, 2H). ^{13}C

NMR δ 209.7, 147.9, 145.8, 142.5, 128.7, 128.6, 126.3, 117.2, 110.7, 53.5, 47.7, 40.2, 38.3, 33.9, 22.1, 19.6; EI-HRMS *m/z* calculated for $C_{18}H_{18}O_2$ (M$^+$): 266.1307, found: 266.1304.



***cis*-5a-Vinyl-4,5a,6,7,8,9a-hexahydro-5H-naphtho[1,2-b]furan-9-one (189).** Enone **186** (40 mg, 0.21 mmol) was reacted with excess vinyl cuprate generated from CuI, and vinyl magnesium bromide (0.45 mmol) in THF (0.6 mL), TMSCl, Et_3N (0.5 mL) and TMEDA (0.045 mL, 0.30 mmol). The crude material was isolated and subjected to the same electrolysis conditions as those described for **164** to provide **189** (30 mg, 67%) as a colorless oil. R_f (5:1 Hex:EtOAc) = 0.25; IR (neat) ν_{max} 3082, 2931, 1716, 1502, 1073 cm^{-1}; ^{1}H NMR δ 7.33 (dd, *J* = 0.9, 2.0, 1H), 6.24 (d, *J* = 2.0 Hz, 1H), 5.77 (dd, *J* = 17.0, 11.0 Hz, 1H), 5.12 (d, *J* = 11.0 Hz, 1H), 5.06 (d, *J* = 17.0 Hz, 1H), 3.62 (s, 1H), 2.65-2.40 (m, 2H), 2.35-2.15 (m, 2H), 1.95-1.72 (m, 4H), 1.65-1.50 (m, 2H); ^{13}C NMR δ 209.5, 147.0, 144.2, 142.6, 116.7, 114.3, 110.5, 53.6, 45.5, 39.7, 33.0, 31.6, 22.0, 19.1; EI-HRMS *m/z* calculated for $C_{14}H_{16}O_2$ (M$^+$): 216.1150, found: 216.1157.



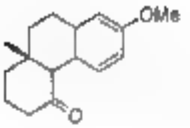
Methoxy-2,3,4a,9,10,10a-hexahydro-1H-phenanthren-4-one (197), (198), 3-[2-(3-Methoxy-phenyl)-ethyl]-cyclohex-2-enone (201). A solution of bromide **192** (590 mg, 2.7 mmol) in THF (2.7 mL) was added to a flask containing magnesium turnings (85 mg, 3.5 mmol) and the mixture was stirred at rt for 2 h. The mixture was cooled to 0°C

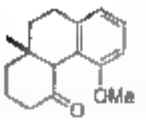
and CuI (51 mg, 0.27 mmol) was added. The mixture was stirred for 5 min before cooling to -78°C. A mixture of TMSCl:Et$_3$N (2.5 mL) was added over 2 min, followed by TMEDA (0.40 mL, 2.7 mmol) and 2-cyclohexen-1-one (0.20 mL, 2.1 mmol). The reaction was allowed to warm to rt over 6h. Workup and electrolysis followed the same procedure as that described for **3**, except during electrolysis an electrolyte solution with a 1.0 M LiClO$_4$ concentration was used and a current was applied until 2.2 F/mol were passed. After chromatography, a mixture of isomers in a 4:1 ratio was isolated as a colorless oil (165mg, 35%) as well as the unsaturated ketone **190** (82 mg, 17%) after chromatography in gradient (10:1 to 1:1 Hex:EtOAc).

major (**197**): R_f (5:1 hexanes:EtOAc) = 0.30; IR (neat) υ_{max}: 2922, 1708, 1610, 1450, 1257, 1041 cm^{-1}; ^{1}H NMR δ 6.84 (m, 1H), 6.71 (m, 1H), 6.65 (m, 1H), 3.77 (s, 3H), 3.66 (d, J = 5.3 Hz, 1H), 2.82 (m, 1H), 2.46 (m, 1H), 2.36 (m, 2H), 2.00-1.80 (m, 3H), 1.80-1.60 (m, 3H); ^{13}C NMR δ 24.6, 26.1, 28.0, 28.7, 38.1, 40.7, 54.9, 55.3, 112.3, 114.1, 125.2, 130.9, 137.4, 158.5, 212.3; EI-HRMS *m/z* calculated for $C_{15}H_{18}O_2$ (M$^+$): 230.1307, found: 230.1310.

minor (**198**) (partial): ^{1}H NMR ($CDCl_3$) δ 7.14 (t, J = 7.4 Hz, 1H), 3.99 (d, J = 5.5 Hz, 1H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 210.4, 157.6, 137.7, 127.5, 123.4, 121.4, 107.4, 55.6, 50.1, 42.2, 38.6, 30.9, 29.4, 25.2, 24.2.

3-[2-(3-Methoxy-phenyl)-ethyl]-cyclohex-2-enone (201): R_f (2:1 hexanes:EtOAc) = 0.22. IR (neat) υ_{max}: 3105, 2923, 1671, 1629, 1037 cm^{-1}; ^{1}H NMR δ 7.24-7.14 (m, 2H), 6.81-6.70 (m, 2H), 5.91 (s, 1H), 2.79 (t, J = 8.5 Hz, 2H), 2.52 (t, J = 8.5 Hz, 2H), 2.35 (t, J= 6.4, 2H), 2.30 (t, J = 5.7 Hz, 2H), 1.99 (q, J = 6.7 Hz, 2H); ^{13}C NMR δ 199.9, 165.6, 159.8, 142.8, 129.8, 126.2, 120.8, 114.4, 111.1, 55.3, 37.0, 39.7, 33.5, 30.1, 22.9.



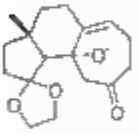


Methoxy-10a-methyl-2,3,4a,9,10,10a-hexahydro-1H-phenanthren-4-one (199), (200). A solution of Grignard reagent **193** (0.65 M, 1.18 mL, 0.77 mmol) was cooled to 0°C and CuI (15 mg, 0.079 mmol) was added. The mixture was stirred for 5 min and then cooled to -78°C. A mixture of TMSCl, Et_3N was added (1.0 mL), followed by TMEDA (0.1.5 mL, 0.77 mmol) and 3-methyl-2-cyclohexen-1-one (0.59 mmol). The reaction mixture was allowed to warm to rt over 6 h. Work up and electrolysis was carried out as describe for the preparation of **164**, except that an electrolyte solution with a 1.0 M $LiClO_4$ concentration was used and the current was applied until 2.2 F/mol were passed. After chromatography the isomers **188** and **189** were isolated as a colorless oil (68mg, 47%, 4:1, **188**:**189**). The two isomers could be separated by repeated chromatography.

major (**199**): R_f (5:1 hexanes:EtOAc) = 0.33; IR (neat) υ_{max} 2921, 1707, 1610, 1502, 1244, 1041 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.80 (d, J=8.2Hz, 1H), 6.72 (m, 1H), 6.68 (m, 1H), 3.77 (s, 3H), 3.26 (s, 3H), 2.90 (t, J = 7.4 Hz, 1H), 2.82 (t, J = 6.1 Hz, 1H), 2.30 (m, 2H), 1.88 (m, 2H), 1.78 (t, J = 6.0 Hz, 1H), 1.71 (t, J=6.4 Hz, 1H), 1.56-1.40 (m, 2H), 1.05 (s, 3H); ^{13}C NMR δ 213.2, 158.3, 136.5, 130.2, 125.2, 114.0, 112.4, 60.9, 55.3, 39.3, 37.6, 33.4, 33.1, 27.1, 26.1, 22.4; EI-HRMS *m/z* calculated for $C_{16}H_{20}O_2$ (M^+): 244.1463, found: 244.1463.

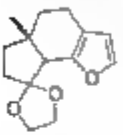
minor (**200**): Rf (5:1 hexanes:EtOAc) = 0.31; IR (neat) υ_{max} 2937, 1710, 1455, 1253, 1047; ^1H NMR δ 7.19 (td, J = 1.0, 7.6 Hz, 1H), 6.76 (m, 1H), 6.71 (m, 1H), 3.80 (s, 3H), 3.73 (s, 1H), 2.59-2.50 (m, 2H), 2.34-2.14 (m, 4H), 1.95-1.84 (m, 2H), 1.72-1.58

(m, 2H), 1.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 22.3, 25.[illegible]3, 30.3, 36.1, 39.0, 4[illegible].2, 44.0, 53.8, 55.4, 111.2, 114.3, 120.9, 129.6, 144.3, 159.3, 212.3; EI-HRMS *m/z* calculated for $C_{16}H_{20}O_2$ (M^+): 244.1463, found: 244.1463.



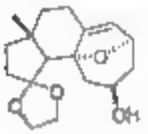
Ketone 209. A 15-mL flask was charged with aceta[illegible] **211** (133 mg, 0.57 mmol). To this was added a CF_3CH_2OH solution of $NaOCH_2CF_3$ (1.5 M, 2.3 mL, 3.5 mmol) and a solution of 1,1,3-trichloroacetone (0.19 mL, 1.8 mmol) in CF_3CH_2OH (1.0 mL) over 3 h. The mixture was stirred overnight. The mixture was then diluted with CH_2Cl_2 and brine. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3*5 mL). The combined organic phases were washed with brine. The solution was dried with $MgSO_4$, filtered and the solvent evaporated. The residue was taken up in MeOH (5 mL) and Zn-Cu couple (800 mg, 12.2 mmol) was added. The mixture was stirred for 3 days at rt. The mixture was diluted with EtOAc (7 mL), filtered though a plug of celite, and the plug of celite was washed with EtOAc. The volatiles were evaporated and the residue was purified by chromatography (2:1 hexanes:EtOAc) to provide **209** as a yellow solid (118 mg, 71%). An analytical sample was crystallized from EtOH:H_2O (white needles): R_f (1:1 hexanes:EtOAc) = 0.32; mp 101-103°C; IR (KBr) ν_{max} 2929, 2872, 1741, 1501, 1163, 1023 cm^{-1}; ^{1}H NMR (500 MHz) δ 5.62 (m, 1H), 4.94 (brd, J = 5.0 Hz, 1H), 4.06 (ddd, J = 6.4, 5.6, 4.0 Hz, 1H), 3.86 (td, J = 6.6, 4.6 Hz, 1H), 3.83 (q, J = 6.5 Hz, 1H), 3.78 (q, J = 6.9 Hz, 1H), 2.73 (dd, J = 16.2, 5.1 Hz, 1H), 2.67 (d, J = 16.0 Hz, 1H), 2.55 (d, J = 16.0 Hz, 1H), 2.51 (dt, J = 16.4, 5.[illegible], 1H), 2.25 (ddd, J = 16.4, 11.0, 5.3, 1H), 2.[illegible]1 (s, 3H), 1.90 (ddd, J = 13.7, 7.5, 3.4, 1H), 1.86

(dd, J = 14.1, 7.4 Hz, 1 H), 1.80 (ddd, J = 13.6, 11.0, 4.7 Hz, 1 H), 1.64 (dt, J = 13.0, 7.7 Hz, 1 H), 1.54 (ddd, J = 13.0, 9.4, 7.4, 4.1 Hz, 1 H), 1.32 (dt, J = 13.6, 5.3 Hz, 1 H), 1.16 (s, 3 H), ^{13}C NMR δ 206.9, 145.6, 120.5, 119.4, 83.8, 76.5, 65.4, 64.8, 57.6, 54.0, 45.9, 40.3, 37.3, 36.8, 32.7, 30.7, 28.5, 21.9; LSIMS-HRMS *m/z* calculated for $C_{19}H_{22}O_4$ (M$^+$) 290.1518, found 290.1498; Anal. Calcd. for $C_{19}H_{22}O_4$: C, 70.32; H, 7.64. found C, 70.08; H, 7.63

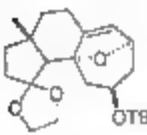


Furyl ketal 211 A dry 5-mL vial containing ketone **3** (150mg, 0.79 mmol) was charged with CH(OEt)$_3$ (0.4 mL) and ethylene glycol (0.4 mL). A steady stream of argon was bubbled through the mixture for 10 min. After this, TsOH•H$_2$O (4 mg, 0.022 mmol) was added and the vial was sealed. The mixture was allowed to stand at rt for 6 h and then diluted with Et$_2$O (5mL) and saturated aqueous NaHCO$_3$ (2 mL). After extraction, the aqueous phase was extracted again with Et$_2$O (2*5 mL), and the combined extracts were washed with brine and dried over MgSO$_4$. After filtration and evaporation of solvent the crude mixture was purified by chromatography (9:1 hexanes: EtOAc) yielding ketal **211** as a white solid (158 mg, 85%): mp 35-36°C; R_f (1:1 hexanes:EtOAC) = 0.25; IR (KBr) ν_{max} 2934, 1560, 1216, 1080, cm^{-1}; ^{1}H NMR δ 7.28 (d, J = 1.9 Hz, 1H), 6.26 (d, J = 1.9 Hz, 1H), 4.10 (ddd, J = 0.9, 6.4, 6.2 Hz, 1H), 3.89 (ddd, J = 1.4, 6.2, 7.1 Hz, 1H), 3.81 (ddd, J = 1.4, 6.4, 6.4 Hz, 1H), 3.61 (ddd, J = 0.9, 6.4, 7.1 Hz, 1H), 2.50-2.40 (m, 2H), 2.75 (s, 1H), 2.04 (t, J = 7.8 Hz, 2H), 1.85 (ddd, J = 2.8, 4.5, 6.9 Hz, 1H), 1.76-1.58 (m, 2H), 1.38 (dt, J = 3.8, 14.4 Hz, 1H), 1.05 (s, 3H); ^{13}C NMR δ 148.4, 141.1, 117.5, 117.3, 110.2, 65.2, 64.3, 53.3, 41.3, 36.8, 36.0, 32.4, 25.9,

19 5, EI-HRMS calculated for $C_{14}H_{18}O_3$ (M): 234 1256, found 234 1245, Anal Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7 74, found: C, 71 82, H, 7 73.

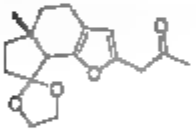


Alcohol 213. A 10-mL flask was charged with a THF solution of L-selectride (1.0 M, 0.22 mL, 0.22 mmol) and cooled to -78°C To this was added the ketone **209** (53 mg, 0 18 mmol) in THF (0 5 mL) over 5 min The cooling bath was removed and 20% NaOH was added (0.2 mL), followed by 30% H_2O_2 (0 1 mL) Water was added (1 mL) and the phases were separated The aqueous phase was extracted with EtOAc (3*2 mL) The combined organic phases were dried with $MgSO_4$, filtered and the solvent was evaporated. The residue was purified by chromatography (1.4 hexanes:EtOAc) to give the alcohol **213** as an oil (49 mg, 92%): R_f (1 4 hexanes EtOAc) = 0.24 , ^{1}H NMR δ 5 78 (brs, 1H), 4 71 (brs, 1H), 4 04 (m, 1H), 3 96 (m, 1H), 3.83-3 70 (m, 3H), 2 61 (dt, J = 16.4, 5 6 Hz, 1H), 2.46-2.32 (m, 2H), 2.25 (ddd, J = 4 1, 6.2, 14 9 Hz, 1H), 2.14-1 92 (m, 3H), 1.86-1 71 (m, 3H), 1 67 1 45 (m, 3H), 1 39 (dt, J = 13.3, 6 2 Hz, 1H), 1 19 (s, 3H); ^{13}C NMR δ 148.6, 122 1, 119 5, 83 4, 66.7, 65 4, 64 8, 57.8, 43 6, 40.3, 37 2, 36.8, 35 2, 32.8, 29 1, 22 8, FAB-HRMS *m/z* calculated for $C_{20}H_{35}O_4Si$ 293 1753 (M+H), found 293 1760.



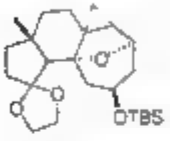
Silyl ether 214. A 5 mL flask was charge with a solution of alcohol **213** (30 mg, 0 10 mmol) in CH_2Cl_2 (1 0 mL). The mixture was cooled to 0°C and 2,6-lutidine (0.0 5

mL, 0.13 mmol) was added followed by TBSOTf (0.030 mL, 0.13 mmol). After stirring for 5 min saturated aqueous $NaHCO_3$ was added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3*2mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered and the solvent evaporated. The residue was purified by chromatography (8:1 hexanes, EtOAc) to yield **214** as a colorless oil (37 mg, 90%): R_f (8:1 hexanes EtOAc) = 0.25. ^{1}H NMR δ 5.51 (brs, 1H), 4.64 (dd, J = 2.2, 2.7 Hz, 1H), 4.06 (m, 2H), 3.82 (m, 2H), 3.72 (m, 1H), 2.49 (dt, J = 16.5, 5.6 Hz, 1H), 2.31 (m, 1H), 2.10 (ddd, J = 14.7, 6.4, 3.8 Hz, 1H), 1.92-1.27 (m, 11H), 1.14 (s, 3H), 0.86 (s, 9H), -0.02 (s, 3H), -0.03 (s, 3H); ^{13}C NMR δ 144.4, 120.8, 119.4, 83.0, 77.7, 65.6, 65.2, 64.5, 58.0, 43.3, 40.5, 37.2, 36.9, 34.7, 32.8, 28.5, 25.7, 22.8, 17.8, -4.9, -5.0. FAB-HRMS *m/z* calculated for $C_{21}H_{35}O_4Si$ (M$^+$) 406.2539, found 406.2567.



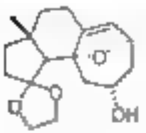
Methyl ketone 215. A 5-mL vial was charged with ketone **209** (7 mg, 0.02 mmol) in 1,2-DME (0.7 mL). To this was added Zn-Cu couple (20 mg, 0.30 mmol) and CH_2I_2 (0.0025 mL, 0.031 mmol). The vial was sealed and placed in an oil bath at 80°C and stirred overnight. The reaction mixture was cooled and filtered through a plug of celite. The celite plug was washed with several small portions of Et_2O. After evaporation of the solvent the residue was purified by chromatography (3:1 hexanes:EtOAc) to yield **215** as a colorless oil (5 mg). R_f (2:1 hexanes, EtOAc) = 0.43, IR (neat) υ_{max} 2926, 1714, 1158, 1019 cm^{-1}. ^{1}H NMR (500 MHz) δ 6.03 (s, 1H), 4.06 (ddd, J = 7.6, 6.6, 5.7 Hz, 1H), 3.88 (dt, J = 7.6, 6.4 Hz, 1H), 3.82 (ddd, J = 7.2, 6.8, 5.8 Hz, 1H), 3.66 (ddd, J = 7.1, 7.1, 6.4 Hz, 1H), 3.65 (s, 2H), 2.73 (s, 1H), 2.43 (ddd, J = 16.2, 6.6, 2.9 Hz, 1H), 2.37 (ddd, J

= 16.4, 5.3, 1.8 Hz, 1H), 2.16 (s, 3H), 2.02 (dd, J = 8.9, 7.2 Hz, 2H), 1.85 (ddd, J = 13.4, 11.0, 6.8 Hz, 1H), 1.68 (dt, J = 12.9, 9.0 Hz, 1H), 1.62 (d, J = 6.6 Hz, 1H), 1.37 (dddd, J = 13.1, 4.9, 2.7, 0.6 Hz, 1H), 1.06 (s, 3H); ^{13}C NMR δ 204.7, 148.4, 146.9, 118.7, 117.8, 109.1, 65.2, 64.5, 53.4, 43.7, 41.4, 36.8, 36.1, 32.2, 29.1, 26.0, 19.6; FAB-MS *m/z* 290 (M^+), 247 (M-CH_3CO^+).

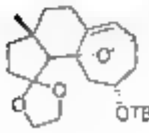


Cyclopropane 216. A 10-mL flask was charged with silyl ether **214** (14 mg, 0.034 mmol) in 1,2-DME (0.50 mL). A solution of Et_2Zn in hexane (1.0 M, 0.85 mL, 0.85 mmol) was added followed by CH_2I_2 (0.137 mL, 1.7 mmol) over 5 min. The reaction vessel was sealed and heated in an oil bath at 70°C for 2 h. The mixture was cooled and saturated aqueous NH_4Cl was added (1.5 mL) slowly, followed by Et_2O (1.5 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3*2mL). The combined organic phases were dried with Na_2SO_4, filtered and the solvent evaporated. The residue was purified by chromatography to give the cyclopropane **216** as an oil (5 mg, 35%): R_f (4:1 hexane: EtOAc) = 0.35; ^{1}H NMR (500 MHz) δ 3.96 (m, 1H), 3.94 (m, 1H), 3.92 (m, 1H), 3.90 (m, 1H), 3.78 (m, 1H), 3.75 (m, 1H), 2.24 (dt, J = 14.6, 1.6 Hz, 1H), 2.13 (td, J = 13.3, 2.7 Hz, 1H), 2.04 (dt, J = 14.2, 4.5 Hz, 1H), 1.86 (s, 1H), 1.77 (m, 2H), 1.71 (td, J = 13.2, 3.9 Hz, 1H), 1.61 (dd, J = 14.6, 5.0 Hz, 1H), 1.58 (dd, J = 7.2, 3.4 Hz, 1H), 1.55 (m, 2H), 1.49 (m, 1H), 1.23 (s, 3H), 1.19 (m, 1H), 1.04 (td, J = 3.6, 0.9 Hz, 1H), 0.86 (s, 9H), 0.10 (dd, J = 7.4, 3.9 Hz, 1H), 0.01 (s, 3H), -0.01 (s, 3H); ^{13}C NMR δ 118.0, 79.1, 76.3, 65.3, 64.9, 64.1, 60.4, 44.8, 41.2, 39.7, 38.7, 37.2, 36.2, 31.7, 30.9

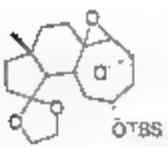
27 2, 24 3, 18 2, 14 7, 0.1 -4.8; FAB-HRMS *m/z* calculated for $C_{24}H_{41}O_4Si$ (M+H$^+$): 421 2774 found: 421 2769



Alcohol 217 To the ketone **209** (2 mg, 0.073 mmol) was added with *i*-PrOH (0 14 mmol), and the mixture was freeze-thawed degassed A THF solution of SmI_2 (0 M, 1 8 mL, 0 8 mmol) was added. The mixture was heated under reflux for 4h. The mixture was cooled and water was added (1 mL). The mixture was filtered through a plug of celite, and the celite was washed with several small portions of EtOAc and water The phases were separated, and the aqueous phase was extracted with EtOAc (3*2 mL). The combined organic phases were washed with saturated $Na_2S_2O_3$ and then brine. The solution was dried with $MgSO_4$, filtered and the solvent evaporated The residue was purified by chromatography (EtOAc) to provide the alcohol **217** as an oil (17 mg, 81%) R_f (EtOAc) = 0 27, ^{1}H NMR δ 5.48 (brs, 1 H), 4 71 (brs, 1 H), 4.03 (t, *J* 5.8 Hz, 1 H), 3.78 (m, 4 H), 2 49 (dt, *J* 16.8, 5.6 Hz, 1 H), 2 28 (m, 1 H), 2 23 (dd, *J* = 12.9, 6 5 Hz, 1 H), 2 01 (s, 1 H), 1 94 1 72 (m, 4 H), 1 66-1 44 (m, 3 H), 1 42-1 24 (m, 2H), 1 19 (s, 3H), ^{3}C NMR δ 143.4, 119.4, 118 5, 83 9, 77 6, 65 4, 65.3, 64 8, 57 7, 42 8, 40.4, 37 2, 36 8, 36.2, 33.0, 29 1, 21 7 LSIMS-HRMS *m/z* calculated for $C_{18}H_{25}O_4$ (M+H$^+$) 293 1753, found 293 1745

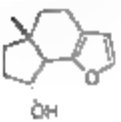


Silyl ether 218. A solution of alcohol **217** (19 mg, 0.065 mmol) in CH_2Cl_2 (0.5 mL) was cooled to 0°C and 2,6-lutidine (0.022 mL, 0.20 mmol), was added followed by TBSOTf (0.030 mL, 0.13 mmol). The mixture was allowed to warm to rt over 2 h, and diluted with CH_2Cl_2. The solution was filtered through a plug of silica gel, and the plug was washed with CH_2Cl_2. After evaporation of the solvent the residue was purified by chromatography (5:1 hexanes:EtOAc) to provide **218** as a colorless oil (22 mg, 83%): R_f (5:1 hexanes:EtOAc) = 0.23; ^{1}H NMR δ 5.49 (brs, 1H), 4.66 (brs, 1H), 4.05 (m, 1H), 3.86-3.68 (m, 4H), 2.50 (dt, J = 16.4, 5.6 Hz, 1H), 2.31-2.18 (m, 2H), 2.06-1.98 (4 line m, 2H), 1.83-1.42 (m, 8H), 1.30 (dt, J = 13.3, 5.6 Hz, 1H), 1.18 (s, 3H), 0.86 (s, 9H), 0.00 (brs, 6H); ^{13}C NMR δ 143.3, 119.5, 78.6, 83.9, 77.7, 65.8, 65.5, 64.9, 57.8, 42.9, 40.4, 37.2, 36.9, 36.3, 33.2, 29.2, 26.1, 25.9, 21.8, 18.3, -4.3 (2C). EI-HRMS *m/z* calculated for $C_{23}H_{38}O_4Si$ (M^+): 406.2539, found: 406.2544

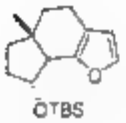


Epoxide 219. A 5-mL vial was charged with ketone (22 mg, 0.054 mmol) in CH_2Cl_2 (0.5 mL). The solution was cooled to -10°C and $NaHCO_3$ (18 mg, 0.22 mmol) was added, followed by *m*CPBA (27 mg, 0.11 mmol). The mixture was stirred for 5 min and then diluted with Et_2O (2 mL). Saturated aqueous $Na_2S_2O_3$ (1 mL) and $NaHCO_3$ (1 mL) solutions were added and the mixture was stirred for 10 min. The layers were separated and the aqueous phase was extracted with Et_2O (2*2 mL). The combined organic phases were washed with $NaHCO_3$, brine and then dried with Na_2SO_4. After removal of the solvent the product **219** was isolated as a colorless oil (20 mg, 87 %): R_f (2:1 Hex:EtOAc) = 0.56. ^{1}H NMR δ 4.19 (m, 1H), 4.08 (m, 1H), 4.00 (m, 1H), 3.94-

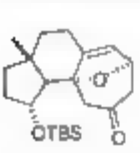
3.82 (m, 2 H), 3.75 (m, 1 H), 3.42 (s, 1 H), 2.24 (dd, J = 13.3, 6.2, 1 H), 2.04 (m, 3 H), 1.86-1.42 (m, 9 H), 1.28 (s, 3 H), 0.87 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR δ 117.5, 77.5, 73.3, 65.9, 64.9, 64.1, 63.3, 58.6, 58.3, 45.6, 39.7, 38.9, 36.3, 36.0, 35.7, 30.9, 26.0, 22.2, 18.3, -4.3, -4.3; LSIMS-HRMS *m/z* calculated for $C_{23}H_{39}O_4Si$ (M+H)$^+$: 423.2567, found: 423.2573



5a-Methyl-5,5a,6,7,8,8a-hexahydro-4H-1-oxa-as-indacen-8-ol (222). A solution of solution of L-selectride (1.0 M, 1.0 mL, 1.0 mmol) was cooled to -78°C. To this was added the ketone **3** (0.35 g, 0.7 mmol) in THF (1.0 mL) over 30 min. After stirring for 2 h, the mixture was warmed to 0° and 20% NaOH (10 mL) was added. An aqueous solution of 30% H_2O_2 (5 mL) was then added over 30 min. The mixture was warmed to rt and extracted with EtOAc. The organic layer was dried on $MgSO_4$. The crude product was purified by chromatography (7:1 hexanes:EtOAc) to give **222** as a colorless oil (0.2 g, 88%). An analytical sample was prepared by freezing under vacuum, followed by trituration with cold pentane to give a white solid: mp 40-41°C; R_f (dichloromethane) = 0.32, (9:1 hexanes:EtOAc) = 0.27; IR (KBr pellet) υ_{max} 3545, 3358, 2951, 1505, 1054 cm^{-1}; ^{1}H NMR δ 7.31 (dd, J = 2.0, 0.6 Hz, 1H), 6.24 (d, J = 2.0 Hz, 1H), 4.51 (m, 1H), 2.64 (d, J = 5.4 Hz, 1H), 2.43 (m, 2H), 2.00 (m, 1H), 1.80 (m, 3H), 1.58 (m, 2H), 1.43 (brs, 1H), 1.06 (s, 3H); ^{13}C NMR δ 149.0, 141.9, 120.0, 110.5, 75.1, 51.3, 41.9, 38.1, 35.5, 33.4, 27.3, 19.9; FAB-MS *m/z* 249 (M+H)$^+$; Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.97, H, 8.39; found: C, 75.02, H, 8.42

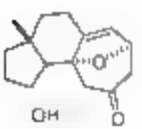


***tert*-Butyl-dimethyl-(5a-methyl-5,5a,6,7,8,8a-hexahydro-4H-1-oxa-as-indacen-8-yloxy)-silane (223).** A solution of alcohol **222** (428 mg, 2.23 mmol) in CH_2Cl_2 (5 mL) was cooled to 0° C, and 2,6-lutidine (0.40 mL, 3.5 mmol) was added, followed by TBSOTf (0.96 mL, 4.2 mmol). The mixture was allowed to warm to rt and stirred for 3h, then diluted with water (5.0 mL) and Et_2O (15 mL). The phases were separated and the aqueous phase was extracted with hexane (3*5 mL). The combined organic phases were washed with saturated $NaHCO_3$ and brine. The solution was dried with $MgSO_4$, filtered and the solvent evaporated. The residue was purified by chromatography (hexanes) to provide **223** as a colorless oil (556 mg, 82%). R_f (hexanes) = 0.37. IR υ_{max} 2954, 1505, 1253, 1075 cm^{-1}. ^1H NMR δ 7.24 (d, J = 1.9 Hz, 1H), 6.17 (d, J = 1.9 Hz, 1H), 4.46 (dt, J = 1.4, 4.0 Hz, 1H), 2.45 (d, J = 4.9 Hz, 1H), 2.36 (8 line m, 2H), 1.03 (s, 3H), 0.70 (s, 9H), -0.04 (s, 3H), -0.23 (s, 3H); ^{13}C NMR δ 150.2, 140.5, 118.2, 110.3, 75.7, 51.7, 41.7, 39.1, 36.1, 34.9, 26.9, 25.7, 20.1, 17.9, -4.9, -5.4; EI-MS *m/z* 306 (M^+), 249 (M $C(CH_3)_3^+$). Anal. Calcd. for $C_{18}H_{30}O_2Si$: C, 70.53; H, 9.87; found: C, 70.49; H, 9.94.

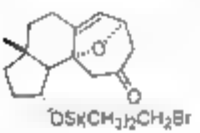


Ketone 224. A dry 50-mL flask and stirrer bar was charged with furan **223** (1.1g, 3.6 mmol). The sample was dried thoroughly under vacuum and purged with argon. To this was added portionwise and simultaneously 1,1,3,-trichloroacetone (1.1mL, 10.5 mmol) and a CF_3CH_2OH solution of $NaOCH_2CF_3$ (1.6 M, 13.5mL, 21.5 mmol), where ca. 10% the initial volume of each mixture was added every 15 min. After the addition

was complete, stirring was continued for 1 5 h. The mixture was diluted with CH2C.2 (20mL) and brine (10 mL). The phases were separated and the aqueous phase was extracted w th CH2C12 (3* .0 mL), and the combined organic phases were washed with brine The solution was dried with MgSO4. fi tered and the solvent evaporated. The crude residue was taken up in MeOH (30 mL) and Zn-Cu couple (9.4 g, 144 mmol) was added. The mixture was sonicated for 8 h, stirred for .2 h and sonicated for another .0 h. The temperature of the mixture was never al owed to exceed ca 40°C The mixture was poured into EtOAc (30 mL) and filtered through a bed of cel te The ce ite pad was wahed w th EtOAc and the solvent was evaporated. The residue was partitioned between saturated aqueous NH_4Cl and CH_2Cl_2 The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3*10 mL). The combined organic phases were washed with brine. The so.ution was dried with MgSO4, filtered and the solvent evaporated The residue was purified by chromatography (9 1 hexanes: EtOAc) to provide **224** as a white solid (942 mg, 72%): mp 84-86° C, R_f (9 1 hexanes. EtOAc) = 0 23, IR (KBr) υ_{max} 2956, 2855, 1717, 251, 1086; ^{1}H NMR δ 5.49 (br s, 1H), 4 92 (d, J = 4.6 Hz, 1H), 4.47 (t J = 3 6 Hz, 1H), 2 67 (d, J = 15 9 Hz .H), 2.45 (d, J = 5 9 Hz, 1H), 2 42 (dt, J = 10.3, 4 6 Hz, 1H). 2 25 (d, J = .6.4 Hz, .H), 2.16 (m, 1H,, 2 03 .dt, J = 4 1, 12.3 Hz), 1 88 (m, 1H), 1 77-1 51 (m, 4H), 1 41 (dt, J = 12 8, 4 1 Hz, 1H), 1 13 (s, 3H), 0.83 (s, 9H), 0 03 (s, 3H), -0 01 (s, 3H); ^{13}C NMR δ 207.6, 146.3, 120 4, 84 2 76 5, 76 2, 57 9, 54 2, 45 9, 40 7, 40 4, 35 9, 34.1, 29 3, 26.0, 22 5, 18 ., -4 6 -4 9 EI-MS m/z 362 (M), 305 (M $C(CH_3)_3^+$); Anal Calcd. for $C_{18}H_{34}O_3Si$ C, 69.56, H, 9 45 found C, 69 44, H, 9.46.

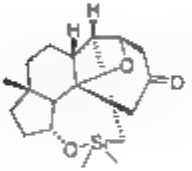


Hydroxy-ketone 225 A 15 mL polypropylene centrifuge tube containing a magnetic stirring vane was charged with the ketone **224** (655mg, 1.81 mmol) in THF (3mL). The mixture was cooled in an ice bath and stirred. HF•pyridine (70 % HF, 1.5 mL) was then added via a plastic syringe. The mixture was sealed and allowed to warm to rt. After stirring for 4h the mixture was added *via* Pasteur pipette to a cooled mixture of ether (50mL) and saturated $NaHCO_3$ (30mL) and stirred vigorously for 20 min while warming to rt. After a second extraction with ether (20mL), the combined extracts were washed with $NaHCO_3$ and then brine. After drying with $MgSO_4$ and evaporation of the solvent, the red solid was recrystallized from hexane: ethyl acetate, yielding **225** as a white solid (415mg, 92%): mp 130-132°C, R_f (1:1 hexanes:EtOAc) = 0.32; IR (KBr) υ_{max} 3527, 2943, 1708, 1307, 1081, 1014 cm-1; ^{1}H NMR δ 5.68 (m, 1H), 5.03 (m, 1H), 4.61 (m, 1H), 2.79 (brs, 1H), 2.73 (dd, *J* = 16.4, 5.0 Hz, 1H), 2.69 (d, *J* = 16.4 Hz, 1H), 2.59 (d, *J* = 15.7 Hz, 1H), 2.48 (dt, *J* = 15.7, 2.0 Hz, 1H), 2.30 (d, *J* = 16.4 Hz, 1H), 2.08-1.74 (m, 2H), 2.20 (m, 1H), 1.70 (d, *J* = 5.8 Hz, 1H), 1.50 (m, 2H), 1.12 (s, 3H), ^{13}C NMR δ 205.9, 148.3, 121.5, 85.5, 76.7, 76.6, 57.5, 53.4, 45.4, 41.6, 40.6, 34.3, 31.3, 27.7, 22.5, FAB-MS *m/z* 249 ($M+H^+$); Anal. Calcd. for $C_{14}H_{20}O_3$: C, 72.55, H, 8.12, found: C, 72.41, H, 8.13.



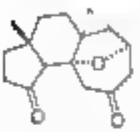
Bromosilylmethyl ketone 226. A 5-mL vial was charged with alcohol-ketone **225** (19mg, 0.077 mmol) and dry DMF (0.40mL). To this was added imidazole (16 mg, 0.24 mmol) and then bromomethyldimethylchlorosilane (0.020 mL, 0.15mmol). The vial was sealed, and the mixture was stirred for 2h at room temperature. Hexane (2mL) and water

(2mL) were then added. The aqueous phase was extracted with hexane (3*2mL). The combined hexane extracts were washed with water (2* 0.5 mL) and then filtered through a plug of sodium sulfate. The crude product **226** was obtained as a yellow oil (29 mg, 94%) and was not purified further. Only traces of impurities were detected by TLC and NMR analysis. R_f (hexanes) = 0.35, ^{1}H NMR δ 5.50 (brs, 1H), 4.92 (d, J = 4.9 Hz, 1H), 4.53 (t, J = 3.7 Hz, 1H), 2.60-2.75 (m, 2H), 2.38-2.50 (m, 2H), 2.14 (m, 1H), 2.20 (m, 1H), 1.86-2.10 (m, 2H), 1.52-1.80 (m, 4H), 1.39 (dt, J = 13.1, 5.6 Hz, 1H), 1.12 (s, 3H), 0.27 (s, 3H), 0.23 (s, 3H), 0.21 (s, 3H), 0.17 (s, 3H), ^{13}C NMR δ 207.2, 147.1, 119.1, 84.3, 76.6, 57.6, 54.0, 46.0, 40.8, 40.2, 35.6, 34.0, 29.5, 22.4, 17.2, -2.7, -2.9, LSIMS-HRMS *m/z* calculated $C_{18}H_{25}BrO_3Si$ (M+H$^+$): 399.099., found: 399.0996



Ketone 227 In a dry 5-mL flask containing a magnetic stirring bar was added methylbromosiloxane **226** (11mg, 0.028mmol) in an AIBN stock solution of benzene (4.5mg/20mL, 2.0mL). The solution was freeze-thaw degassed with argon three times. A Claisen adapter with a condenser on the outer neck and septa on the inner neck was attached. The solution was brought to a gentle boil under reflux as a solution of Bu_3SnH (0.0081mL) in benzene (0.9mL, degassed) was added *via* a syringe, needle and syringe pump over 6 h. The mixture was heated another 1 h after addition. Upon cooling the benzene was evaporated and the residue was dissolved in ether. The ether was washed twice with 1% NH_4OH, dried and the solvent removed under vacuum. Purification by chromatography (1g silica, 7:1 hexane: ethyl acetate) provided recovered starting

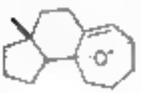
material **226** (4mg) and the product **227** as a colorless oil (5mg): R_f (5:1 Hex: EtOAc) = 0.33; ^{1}H NMR δ 4.46 (brs, 1H), 4.25 (d, J = 6.8 Hz, 1H), 2.65 (dd, J = 17.6, 6.8 Hz, 1H), 2.54-2.38 (m, 3H), 2.31 (d, J = 17.6 Hz, 1H), 2.20-1.84 (m, 2H), 1.80 (m, 1H), 1.69 (d, J = 4.0 Hz, 1H), 1.60-1.35 (m, 5H), 1.05 (s, 3H), 0.86 (m, 1H), 0.53 (dd, J = 2.4, 13.5 Hz, 1H), 0.24 (s, 3H), -0.06 (s, 3H).



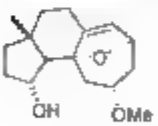
Diketone 228. A 5-mL flask was charged with a $CH_2(CH_2)_2Cl$ solution of Et_2Zn (1.0 M, 0.78 mL, 0.78 mmol). The solution was cooled to 0° C, and CH_2I_2 (0.08 mL, .34 mmol) was added over 2 min. The mixture was stirred for 5 min and the alcohol **225** (9 mg, 0.36 mmol) in $CH_2(CH_2)_2Cl$ (0.20 mL) was added. The mixture was allowed to warm to rt and stirred for 5h. A saturated aqueous NH_4Cl (1.0 mL) solution was added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phases were washed with saturated aqueous $Na_2S_2O_3$, dried with $MgSO_4$, filtered and the solvent evaporated. The residue was purified by chromatography (1:1 to 1:2 hexanes:EtOAc) to provide **228** as an oil (7 mg): R_f (1:2 hexanes:EtOAc) = 0.26, ^{1}H NMR (500 MHz) δ 4.50 (dd, J = 5.2, 1.0 Hz, 1H), 2.95 (dd, J = 15.7, 1.4 Hz, 1H), 2.74 (dd, J = 15.7, 4.8 Hz, 1H), 2.48 (ddd, J = 18.7, 12.3, 9.1 Hz, 1H), 2.44 (d, J = 13.7 Hz, 1H), 2.34 (dt, J = 15.8, 1.4 Hz, 1H), 2.32 (ddt, J = 18.7, 8.1, 1.6 Hz, 1H), 2.12 (s, 1H), 2.01 (dddd, J = 13.8, 12.3, 4.6, 1.7 Hz, 1H), 1.85 (ddd, J = 13.0, 9.0, 1.9 Hz, 1H), 1.77 (td, J = 12.0, 4.9 Hz, 1H), 1.65 (td, J = 12.6, 8.3 Hz, 1H), 1.62 (dddd, J = 13.7, 4.1, 3.1, 0.8 Hz, 1H), 1.50 (ddd, J = 7.5, 2.9, 0.5 Hz, 1H), 1.34 (ddd, J = 13.7, 4.1, 3.1 Hz, 1H), 1.31 (s, 3H), 0.77 (ddd, J = 4.3, 3.0, 1.5 Hz, 1H), 0.07 (dd, J = 7.5, 4.2 Hz, 1H), ^{13}C NMR

δ 215.8, 206.8, 77.4, 75.9, 61.2, 52.2, 46.9, 41.9, 37.8, 36.4, 34.4, 32.1, 29.8, 24.6, 23.8, 11.0; EI-HRMS *m/z* calculated for $C_{16}H_{20}O_3$: 260.1412, found: 260.1404

Alcohol-silyl ether 230. A solution SmI_2 was prepared in THF (3.0 mL) from Sm metal (300 mg, 2.0 mmol) and ICH_2CH_2I (495 mg, 1.8 mmol) using the procedure described by Hoffmann.[87] When the formation of SmI_2 was complete, the ketone **224** (315 mg, 0.87 mmol) and 2-propanol (0.067 mL, 2.0 mmol) in THF (0.87 mL) were added to the deep blue solution. The mixture was heated under reflux for 1 h. Water (5 mL) was added to the mixture, and it was filtered through a pad of celite. The pad of celite was washed with several small portions of EtOAc and water. The layers were separated and the aqueous phase was extracted twice with EtOAc. The combined organic layers were washed with brine. After drying with $MgSO_4$ and removal of solvent, the residue (276 mg) was purified by chromatography (2:1 hexanes:EtOAc), providing **230** as a colorless oil (240 mg, 76%): R_f (2:1 hexanes:EtOAc) = 0.25; ^{1}H NMR δ 5.33 (brs, 1 H), 4.69 (brs, 1 H), 4.40 (t, J = 3.5 Hz, 1 H), 3.82 (m, 1 H), 2.39 (dt, J = 15.2, 4.7 Hz), 2.21 (dd, J = 12.4, 6.2 Hz, 1 H), 2.16 (m, 1 H), 2.02 (m, 1 H), 1.95-1.80 (m, 3 H), 1.68-1.48 (m, 5 H), 1.43-1.24 (m, 3 H), 1.15 (s, 3 H), 0.81 (s, 9 H), 0.00 (s, 3 H), -0.05 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 144.1, 118.2, 84.2, 77.8, 76.2, 65.7, 58.3, 43.2, 40.7, 40.5, 36.5, 36.2, 34.1, 29.7, 26.1, 22.5, 18.1, -4.7, -4.9; EI-HRMS *m/z* calculated for $C_{21}H_{36}O_3Si$ (M^+): 364.2434, found: 364.2432.

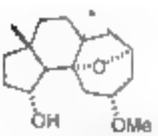


methyl ether-silyl ether 231. A 5-mL flask containing hexane washed NaH (18 mg, 0.75 mmol) was charged with the alcohol **230** (123 mg, 0.34 mmol) in THF (1.5 mL). The mixture was heated under reflux for 30 min, and MeI (0.2 mL, 3.2 mmol) was added. The mixture was heated under reflux for 8h. The mixture was cooled to rt. and water (0.5 mL) was added. The mixture was diluted with Et2O and saturated aqueous NH_4Cl (2 mL). The phase were separated and the aqueous phase was extracted with Et_2O (3*5 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered and the solvent was evaporated. The residue was purified by chromatography to provide **231** as a colorless oil (116 mg, 90%). R_f(8:1 Hex:EtOAc) = 0.22, IR (neat) υ_{max} 2933, 1462, 1377, 1087, ^{1}H NMR δ 5.31 (brs, 1 H), 4.69 (brs, 1 H), 4.39 (t, J = 3.3 Hz, 1H), 3.39 (m, 1H), 3.27 (s, 3H), 2.39 (dt, J = 15.4, 5.1, 1H), 2.16 (m, 1H), 2.16 (dd, J = 12.3, 6.2 Hz, 1H), 2.02 (m, 1H), 1.87 (m, 2H), 1.68-1.24 (m, 7H), 1.13 (s, 3H), 0.80 (s, 9H), -0.02 (s, 3H), -0.06 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 144.1, 118.2, 84.0, 76.2, 74.1, 58.3, 55.6, 40.6, 40.4, 39.6, 36.2, 34.0, 32.6, 29.8, 26.0, 22.5, 18.0, -4.7, -4.9, EI-HRMS *m/z* calculated for $C_{22}H_{38}O_3Si$ (M^+) 378.2590, found: 378.2593



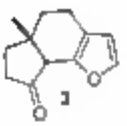
Alcohol-methyl ether 232. A polypropylene eppendorf tube was charged with ether **231** (51 mg, 0.14 mmol) in THF (0.7 mL) and cooled to 0°C. To this was added HF•pyridine (70% HF, 0.2 mL). The mixture was stirred and allowed to warm to rt. After 1 h the mixture was added to $NaHCO_3$ (5 mL) and Et_2O (5 mL). The phases were separated, and the aqueous phase was extracted with Et_2O (2* 2mL). The combined organic phases were washed with $NaHCO_3$, dried with $MgSO_4$, filtered, and the solvent

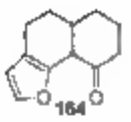
evaporated. The residue was purified by chromatography (2:1 hexanes:EtOAc) to provide **221** (23 mg, 64 %) as an oil. R_f (2:1 hexanes:EtOAc) = 0.29; ^{1}H NMR δ 5.53 (br s, 1 H), 4.81 (br s, 1 H), 4.54 (t, J = 4.9 Hz, 1 H), 3.40 (m, 1 H), 3.29 (s, 3 H), 3.04 (s, 1 H), 2.47 (dt, J = 15.7, 4.3 Hz, 1 H), 2.25 (m, 1 H), 2.21 (dd, J = 13.3, 5.7 Hz, 1 H), 2.05-1.38 (m, 10 H), 1.13 (s, 3 H). ^{13}C NMR ($CDCl_3$) δ 146.2, 119.6, 85.5, 77.9, 76.6, 73.4, 57.7, 55.7, 44.6, 40.6, 39.1, 34.7, 32.2, 31.3, 28.1, 22.4. EI-HRMS *m/z* calculated for $C_{16}H_{24}O_3$ (M^+): 264.1725, found: 264.1742.



Cyclopropane 233. For this procedure the solvent was degassed by purging with argon during sonication for 15 min prior to use. A solution of Et_2Zn (0.039 mL, 0.38 mmol) in CH_2Cl_2 (1.2 mL) was cooled to 0° C and CH_2I_2 (0.061 mL, 0.76 mmol) was added. The mixture was stirred for 5 min, and the alcohol **232** (10 mg, 0.038 mmol) was added in a solution of CH_2Cl_2 (0.15 mL). The mixture was allowed to warm to rt and the reaction vessel was sealed. The mixture was stirred overnight. Saturated aqueous NH_4Cl (1 mL) was added, and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2* 2mL), and the combined organic phases were washed with saturated $Na_2S_2O_3$ and brine. The solution was dried with $MgSO_4$, filtered and the solvent evaporated to give the cyclopropane **233** (3 mg) as an oil. R_f (2:1 hexanes:EtOAc) = 0.28; ^{1}H NMR δ 4.48 (4 line m, 1H), 4.19, (brt, J = 3.0 Hz, 1H), 3.67 (m, 1H), 3.36 (s, 3H), 2.51 (ddd, J = 13.4, 5.6, 1.2 Hz, 1H), 2.11-1.84 (m, 4H), 1.80-1.24 (m, 10 H), 1.23 (m, 1H), 1.18 (s, 3H), 0.96 (ddd, J = 4.7, 2.6, 1.2 Hz, 1H), 0.20 (dd, J = 7.6, 5.3 Hz)

APPENDIX
SELECTED SPECTRA

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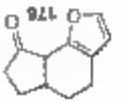

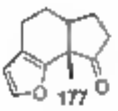
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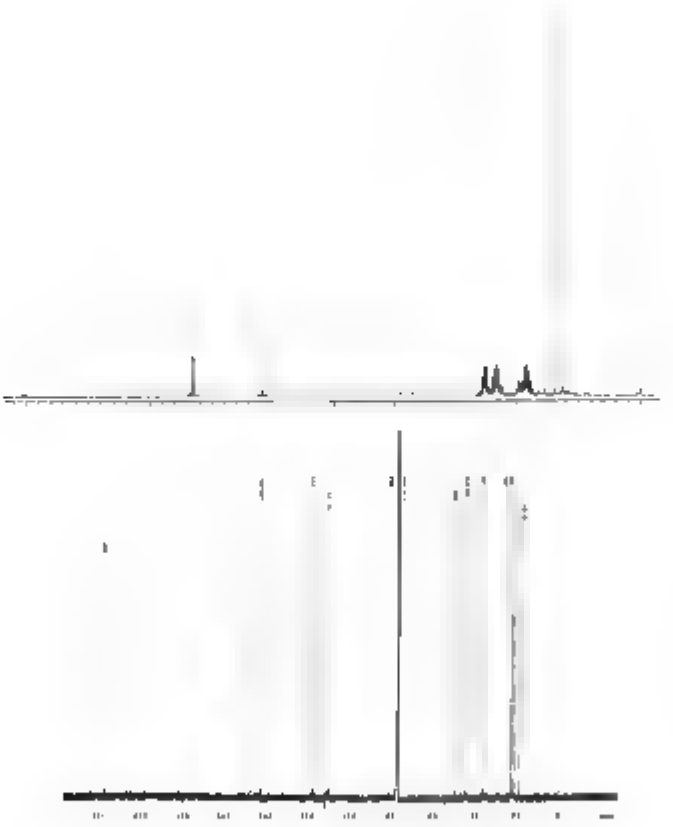

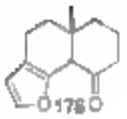
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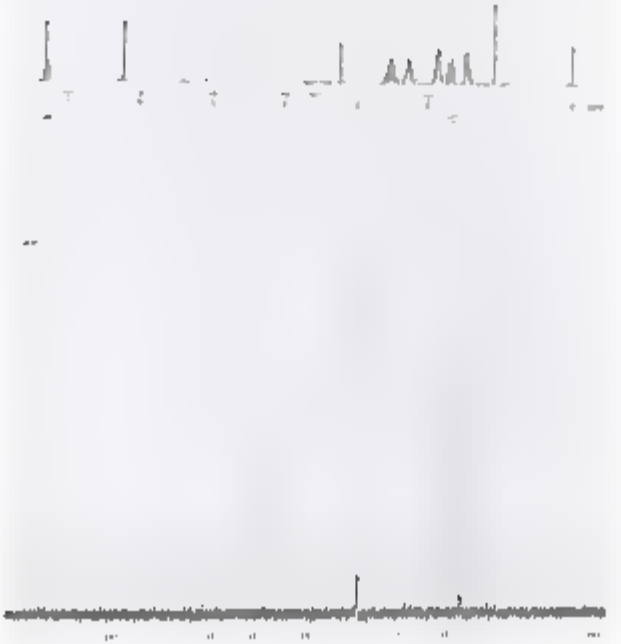

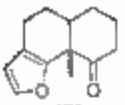

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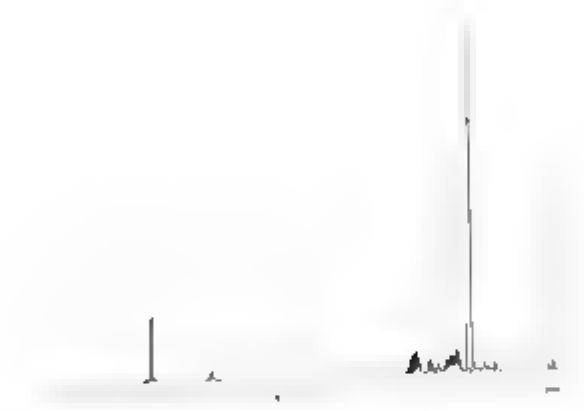

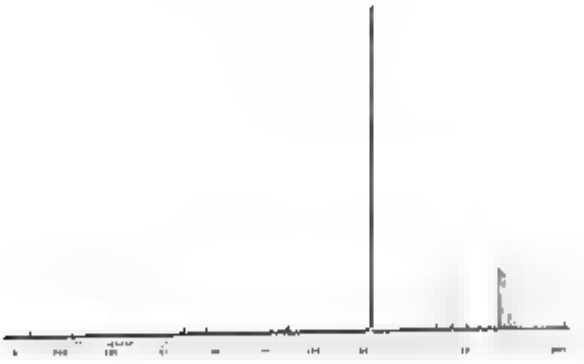

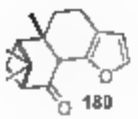

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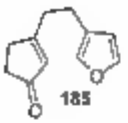

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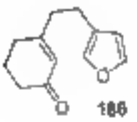

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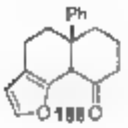
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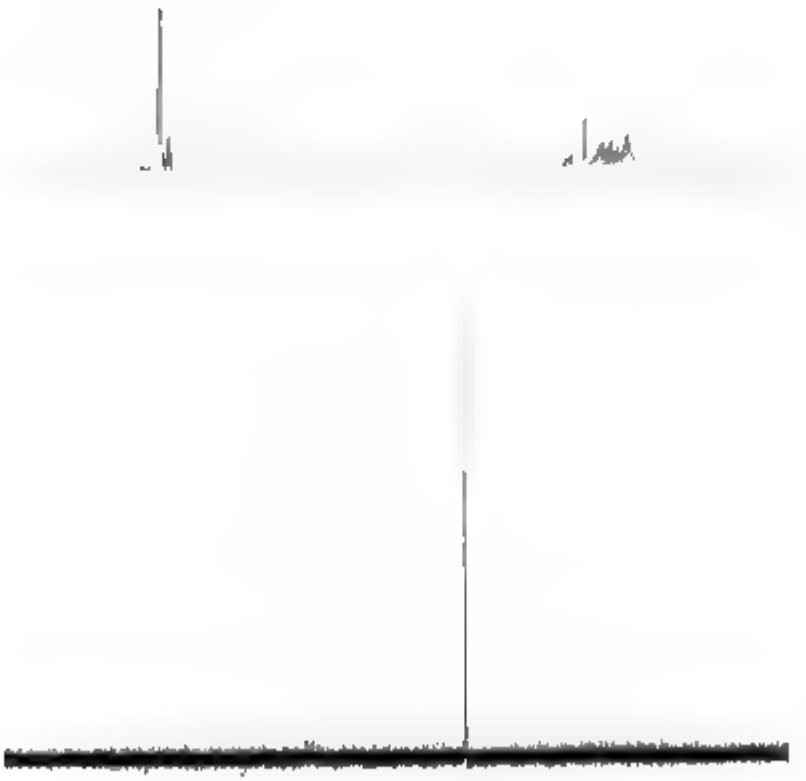

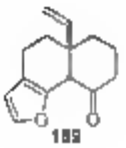

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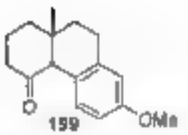

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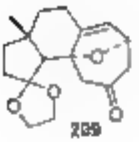

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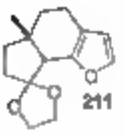

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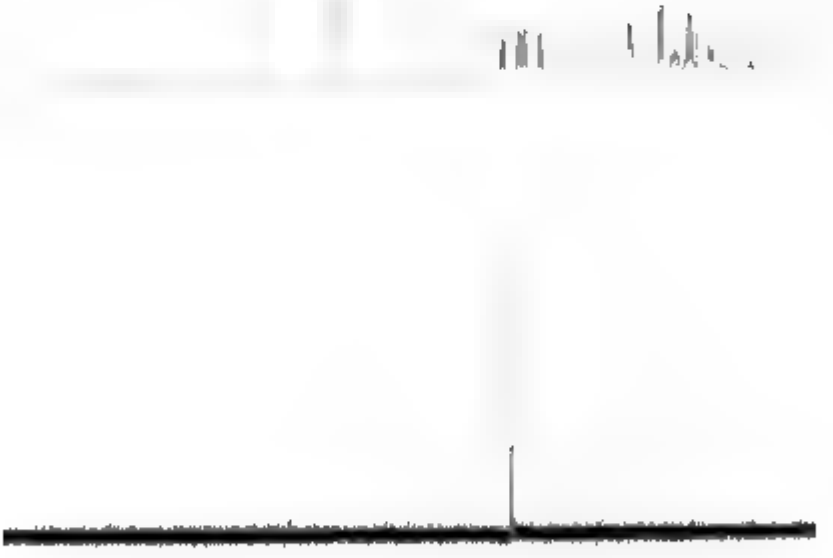

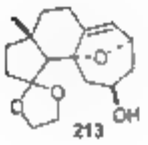

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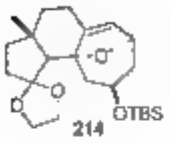

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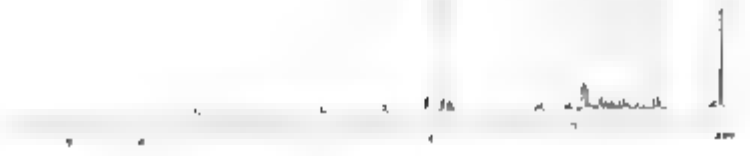

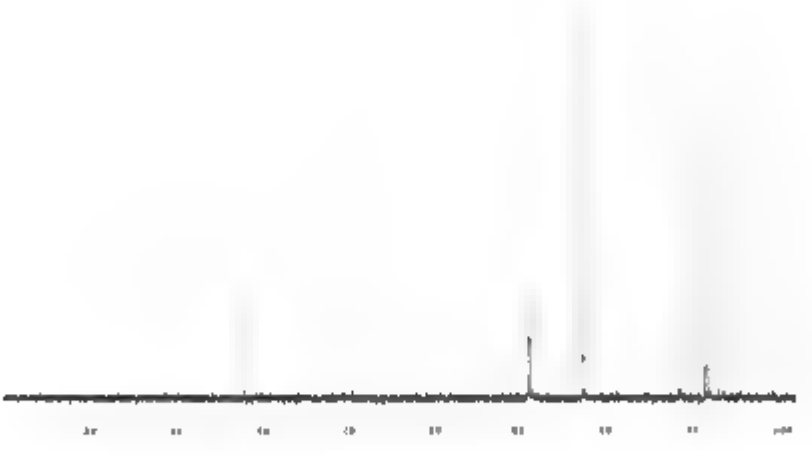

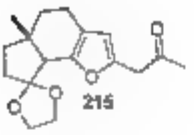
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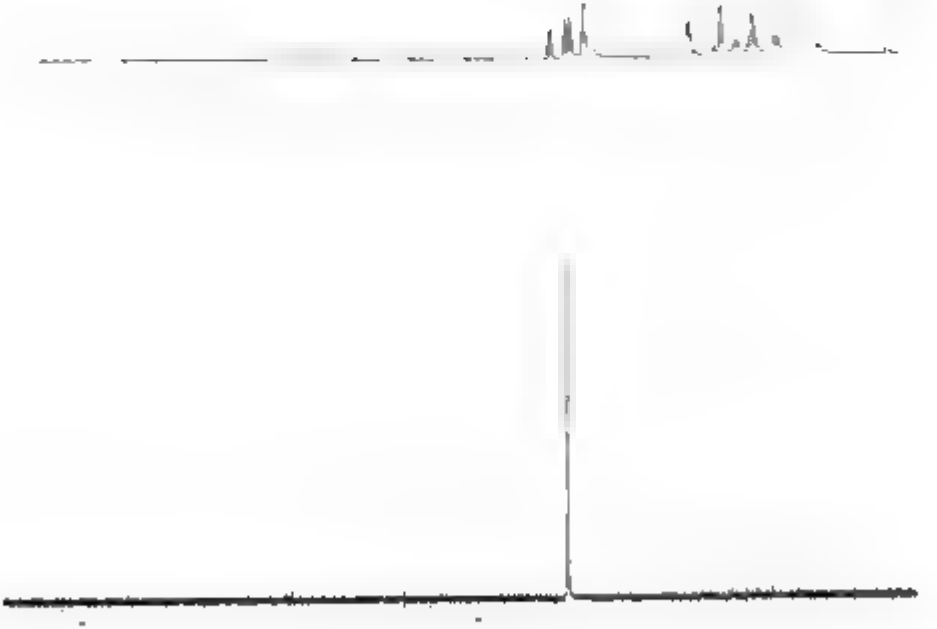

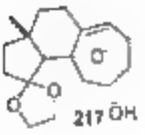
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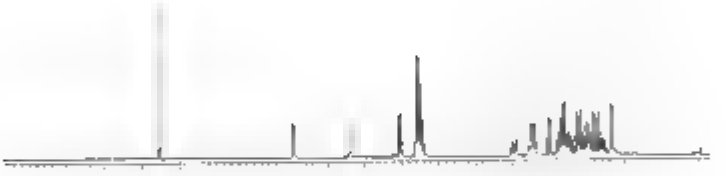

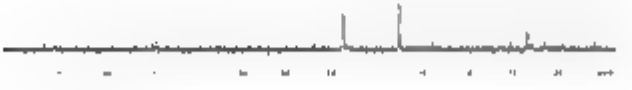

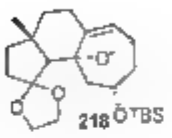
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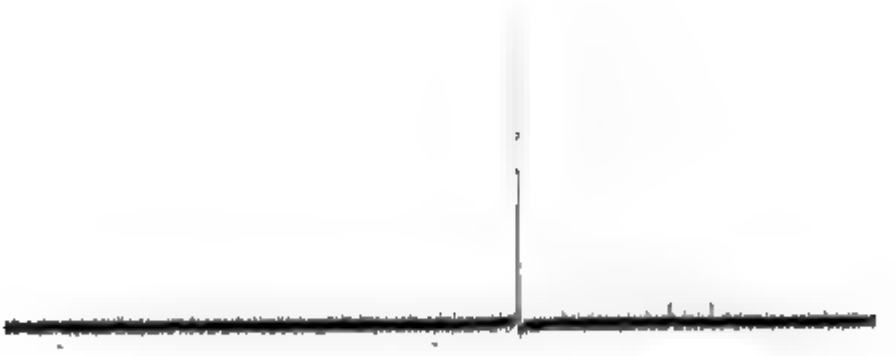

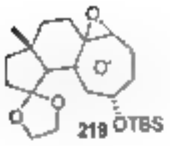
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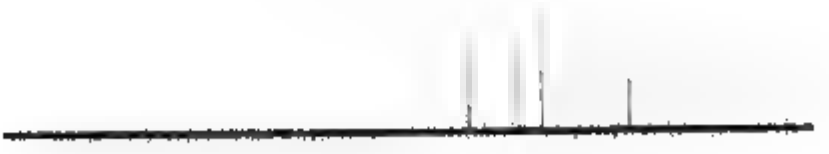

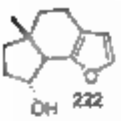

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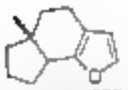

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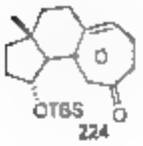
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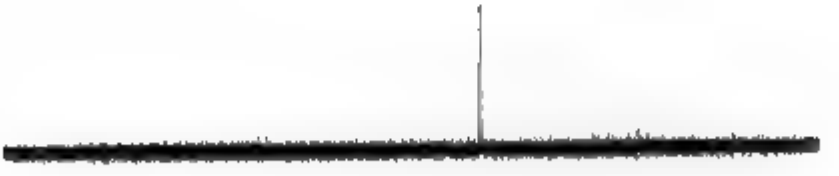

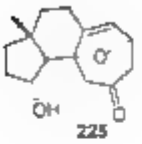

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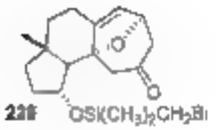

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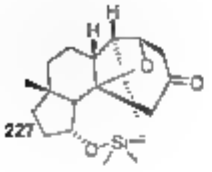
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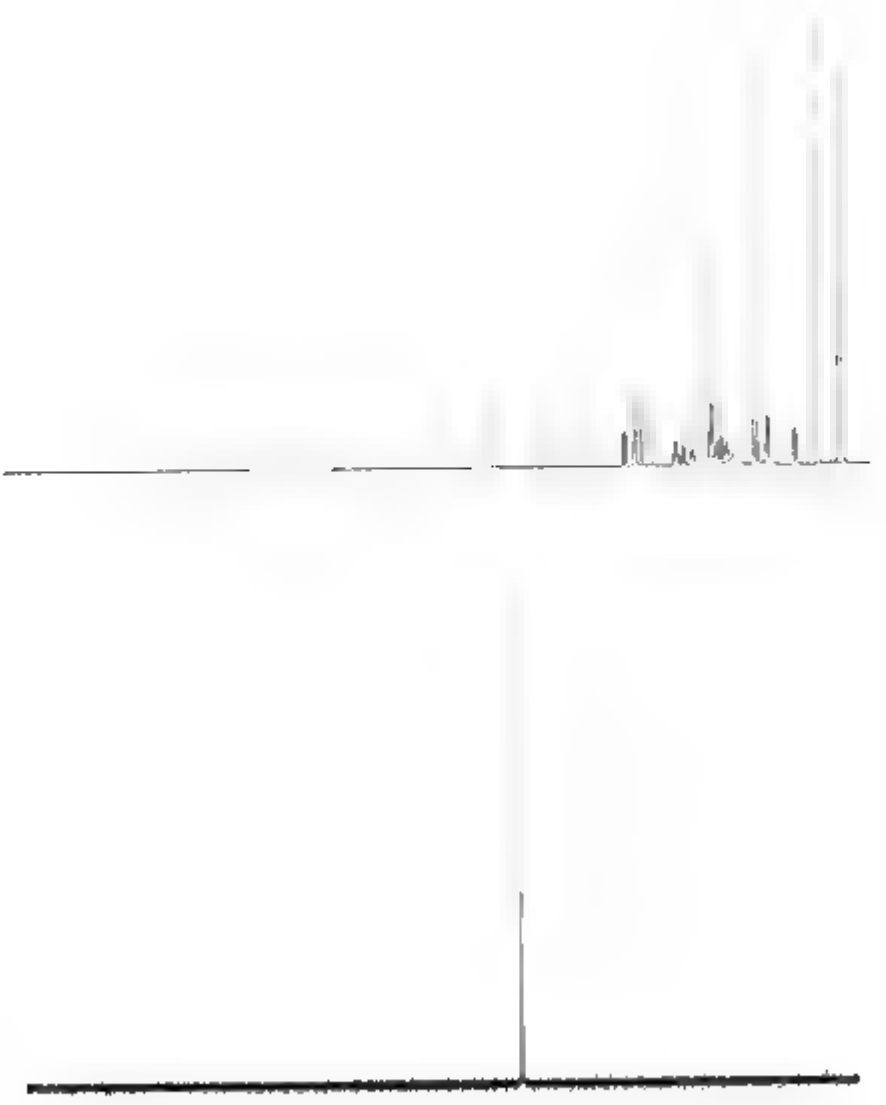

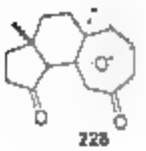

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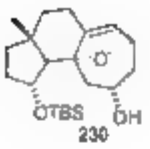

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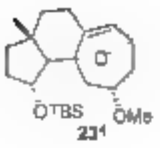

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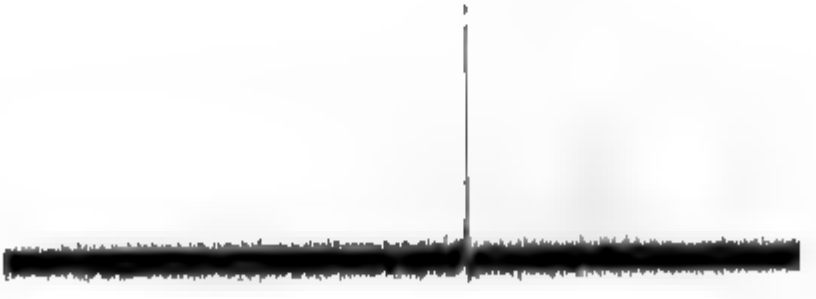

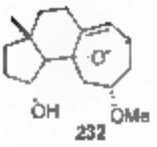

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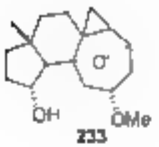

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BIOGRAPHICAL SKETCH

Christopher Robert Whitehead was born in Canton, Illinois in 1973. He lived most of his life from age 4 in and around Atlanta Georgia. He graduated from Forest Park High School in 1992 and received, after majoring in chemistry, a Bachelor of Science degree in 1998 from Georgia State University.

Chris worked with Dr. Paul Franklin as an undergraduate, investigating the synthesis of spirodiketones. He began graduate work with Dr. Dennis Wright at the University of Florida in Gainesville in 1998.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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Associate Professor of Chemistry

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August 2003

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